ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Indocyanine Green Fluorescence Imaging for Colorectal Surgery

A Health Technology Assessment

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Key Messages

What Is This Health Technology Assessment About?

Colorectal surgery is a treatment for a variety of conditions affecting the colon (large intestine) such as colorectal cancer, diverticulitis, and inflammatory bowel disease. This surgery involves *resection*, the removal of a section of the colon, and the creation of an *anastomosis*, which involves surgically connecting the 2 remaining ends of the bowel after the affected part has been removed. One of the most serious complications of colorectal surgery is *anastomotic leak*, when the contents of the bowel leak from the anastomosis into the abdominal space, causing an infection that can spread quickly and become a medical emergency. Assessing *tissue perfusion*, or blood flow, at the planned site of anastomosis is a key step to try to prevent anastomotic leak. The standard approach to assessing anastomotic perfusion involves visual assessment alone, for example, by assessing the colour of the bowel.

Indocyanine green fluorescence imaging (ICGFI) is a technology that involves the use of a fluorescent dye and an imaging system to visualize blood flow. During surgery, the dye is given intravenously and disperses through the blood vessels. When the planned anastomosis site is looked at under near-infrared light, the dye fluoresces bright green, allowing the surgeon to see whether blood flow is adequate.

This health technology assessment looked at how effective and cost-effective ICGFI is when added to colorectal surgery to assess anastomotic perfusion. It also looked at the budget impact of publicly funding ICGFI to assess anastomotic perfusion in colorectal surgery and considered the experiences of patients undergoing colorectal cancer surgery.

What Did This Health Technology Assessment Find?

Compared with visual assessment alone, adding ICGFI to colorectal surgery to assess anastomotic perfusion can help reduce anastomotic leaks, reoperations, and sepsis but may not have much of an effect on hospital readmissions, length of hospital stay, or death.

Compared with visual assessment alone, adding ICGFI to colorectal surgery to assess anastomotic perfusion is cost-effective. We estimate that publicly funding ICGFI to assess anastomotic perfusion in colorectal surgery in Ontario would lead to cost savings of $19.03 million over the next 5 years.

A previously published rapid review evaluating the experiences of patients who had undergone colorectal cancer surgery found no qualitative literature on the patient experience of ICGFI; however, qualitative studies identified anastomotic leak and quality of life as key patient-important outcomes. In the included studies, patients often reported not receiving enough information about surgical outcomes and experiencing anxiety regarding cancer recurrence. We did not conduct direct patient engagement for this health technology assessment since the purpose of the technology is to enhance visualization of the surgical area and because it is expected that patients' preferences and values would align with the potential for improved health outcomes from the use of ICGFI in colorectal surgery.

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A Note About Terminology

Many types of surgeries are performed in the various parts of the colon (large intestine), including the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. In this report, we use the term *colorectal surgery* to refer to surgery involving a *resection* (removal) of any part or parts of the colon (called a *colectomy*), unless otherwise specified. Our analysis focused on colorectal resection surgeries requiring the creation of an *anastomosis*, which involves surgically connecting the 2 remaining ends of the bowel after the affected part has been removed.

Abstract

Background

Both malignant and benign conditions may require colorectal surgery. Anastomotic leak is a serious potential complication, and assessing tissue perfusion at the planned site of anastomosis is critical to try to prevent leaks. The approaches used by surgeons to assess anastomotic integrity and tissue perfusion involve visual assessment of the planned resection area. Indocyanine green fluorescence imaging (ICGFI) is a technology that involves the use of a fluorescent dye and a near-infrared imaging system to allow surgeons to visualize tissue perfusion intraoperatively in real time. We conducted a health technology assessment of ICGFI in colorectal surgery, which included an evaluation of effectiveness, cost-effectiveness, the budget impact of publicly funding ICGFI for the assessment of anastomotic perfusion during colorectal surgery, and the experiences of patients undergoing colorectal cancer surgery.

Methods

We performed a systematic review of the clinical evidence. We assessed the risk of bias of each included study using the Cochrane Risk-of-Bias Tool for randomized controlled trials (RCTs) and the Risk-of-Bias Assessment Tool for Nonrandomized Studies (RoBANS) for nonrandomized studies. We assessed the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted a cost-effectiveness analysis comparing ICGFI with visual assessment alone for the visualization of anastomotic perfusion during colorectal surgery from a public payer perspective. We also analyzed the budget impact of publicly funding ICGFI for colorectal surgery in Ontario. To contextualize the potential value of publicly funding ICGFI for colorectal surgery, we summarized a qualitative literature rapid review conducted by the Canadian Agency for Drugs and Technologies in Health (now Canada's Drug Agency).

Results

We included 6 RCTs and 13 nonrandomized studies in the clinical evidence review. Compared with visual assessment alone, the addition of ICGFI to assess anastomotic perfusion during colorectal surgery reduced anastomotic leaks (GRADE: Low) and reoperations (GRADE: Low) and slightly reduced sepsis, but the evidence for the latter is very uncertain (GRADE: Very low to Low). ICGFI appeared to have little to no effect on hospital readmissions (GRADE: Low) or length of stay (GRADE: Low to Moderate), and its effect on mortality is very uncertain (GRADE: Very low). Our primary economic evaluation found that ICGFI is more effective and less costly than visual assessment alone and is highly likely to be cost-effective at the commonly used willingness-to-pay values of $50,000 and $100,000 per quality-adjusted life-year (QALY). The use of ICGFI could prevent 22 major anastomotic leaks per 1,000 patients undergoing colorectal surgery with anastomosis. With ICGFI, 45 patients would need to be treated to prevent an additional major anastomotic leak. Publicly funding ICGFI to assess anastomotic perfusion in colorectal surgery in Ontario would lead to an annual budget impact ranging from a cost savings of $0.81 million in year 1 to a cost savings of $8.13 million in year 5, for a total 5-year budget impact of $19.03 million in cost savings. We identified a previously published rapid review that found no qualitative literature on the patient experience of ICGFI. However, qualitative studies on the experience of patients who had undergone colorectal cancer surgery identified anastomotic leak and quality of life as key patient-important outcomes. In the included studies, patients often reported not receiving

enough information about surgical outcomes and experiencing anxiety regarding cancer recurrence. We did not conduct direct patient engagement since the purpose of the technology is to enhance visualization of the surgical area and because it is expected that patients' preferences and values would align with the potential for improved health outcomes from the use of ICGFI in colorectal surgery.

Conclusions

The evidence suggests that, compared with visual assessment alone, adding ICGFI to colorectal surgery can help reduce anastomotic leaks, reoperations, and sepsis but may not have an effect on hospital readmissions or length of stay. The effect of ICGFI on mortality is unclear. ICGFI is more effective and less costly than visual assessment alone. We estimate that publicly funding ICGFI for colorectal surgery in Ontario would result in cost savings of $19.03 million over the next 5 years. No literature was found on the patient experience of ICGFI. The qualitative literature on preferences and values for patients who had undergone colorectal cancer surgery identified anastomotic leak and quality of life as key outcomes, with study participants expressing concerns about surgical outcomes and cancer recurrence.

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Objective

This health technology assessment evaluates the effectiveness, cost-effectiveness, and budget impact of publicly funding indocyanine green fluorescence imaging to assess anastomotic perfusion in colorectal surgery. It also considers the experiences of patients undergoing colorectal cancer surgery.

Background

Clinical Need and Population of Interest

Colorectal Surgery

Both malignant conditions (i.e., precancerous and cancerous lesions in the colon) and benign conditions (e.g., diverticulitis, inflammatory bowel disease, bowel obstruction) may require colorectal surgery. Colorectal surgery may involve a colectomy, in which the affected part of the colon is resected (cut out), and the creation of an anastomosis, which involves surgically connecting the 2 remaining ends of the bowel after the affected part has been removed. There are various types of colectomy depending on the part or parts of the bowel being resected, such as right hemicolectomy, left hemicolectomy, transverse colectomy, sigmoid colectomy, low anterior resection, and total colectomy. The location of the resection is dictated by the condition being treated, the location of the tumour, and the presence and extent of any stricture (narrowing), scarring, or severe inflammation.

A colectomy can be conducted as an open, laparoscopic, or robotic-assisted surgery depending on disease complexity and location, patient factors (e.g., body weight, surgical risk), and surgeon experience.

A colectomy typically involves the following steps:

1) Making an incision or incisions in the abdomen (the size and number of incisions depend on whether the procedure is performed open or laparoscopically)
2) Mobilizing the affected part of the colon from its congenital and noncongenital attachments (anatomical connections to other organs and the mesentery, a membrane that holds the intestines in place)
3) Dissecting the mesentery and performing blood vessel ligation (tying off blood vessels to control bleeding)
4) Defining the proximal and distal margins of the affected part of the colon based on perfusion (blood flow) and disease factors
5) Resecting the affected bowel
6) Connecting the ends of the remaining healthy bowel to form an anastomosis

A tension-free and viable anastomosis requires adequate mobility and tissue perfusion where the ends of the bowel have been reconnected. One of the most serious complications of a colectomy is an anastomotic leak, which occurs when the contents of the bowel leak from the newly created

anastomosis into the abdominal space, causing peritonitis, an infection of the abdominal lining. This type of infection can spread quickly, resulting in sepsis (an extreme reaction to an infection and a medical emergency), which increases the risk of morbidity and mortality. The estimated incidence of anastomotic leaks ranges from 1.6% to 14.3% for ileocolic anastomoses, 0.5% to 18% for colorectal anastomoses, and 5% to 19% for coloanal anastomoses, with an overall associated mortality of 12%.[1]

Risk factors for anastomotic leak include poor blood flow at the surgical site, smoking, alcohol consumption, obesity, preoperative use of steroids, male sex, and the presence of comorbidities.[2] The American Society of Anesthesiologists (ASA) Physical Status Classification System can be used together with other factors to predict a patient's perioperative risk. Scores (referred to as *ASA scores*) range from I (1) to VI (6), and higher ASA scores have been associated with an increased risk of anastomotic leak after colorectal surgery.[3]

Assessing tissue perfusion is critical to reducing the risk of anastomotic leak and preventing ischemia (lack of blood supply) to the tissue used in creation of the anastomosis.

Health Conditions

Several health conditions may require a colectomy; the most common are described here.

Colorectal Cancer

Colorectal cancer is a type of cancer that forms in the large intestine in either the colon or rectum. It stems from the abnormal growth of gland cells in the lining of the colon or rectum that form lesions called polyps.[4] Some polyps can be precancerous and, if left untreated, will continue to grow and progress to cancer, which can become metastatic (spread to other parts of the body).[5] Most people with colorectal cancer will need to undergo colorectal surgery to remove precancerous or cancerous polyps, or tumours in more advanced cases.

An Ontario report published in 2022 reported that colorectal cancer was the second-leading cause of cancer deaths (estimated to comprise 10.3% of all cancer deaths in 2022).[6] Colorectal cancer is the fourth most common type of cancer in Ontario after breast, prostate, and lung, and in 2018 accounted for 9.9% of new cancer diagnoses (8,398 cases). Most people with colorectal cancer are diagnosed between the ages of 60 and 79 years. In Ontario, the prevalence of colorectal cancer is projected to increase from 77,097 cases in 2019 to 115,460 cases in 2034.

Diverticulitis

Diverticular disease occurs when the inner lining of the large intestine is pushed out to form multiple diverticula (outpouchings or saclike protrusions) in the lining of the large intestine because of weak spots in the muscle.[7,8] The presence of diverticula is referred to as *diverticulosis*. Most people with diverticulosis do not experience any symptoms, but an estimated 25% will develop symptoms ranging from mild to severe.[7] When diverticula become inflamed or infected, this is referred to as *diverticulitis*, which can result in serious complications including the development of an abscess, fistula, and bowel perforation. After an initial episode of diverticulitis, an estimated 15% to 30% of people will experience recurrence.[8] People who experience recurrent disease or complications such as a fistula or obstruction may require colorectal surgery.

Diverticulosis is estimated to affect 30% to 50% of older adults in industrialized countries, of which 5% are estimated to progress to diverticulitis.[9] Although the incidence of diverticulitis increases with age, over the past few decades the incidence of diverticulitis has increased by 132% among people aged 40 to 49 years.

Inflammatory Bowel Disease

Inflammatory bowel disease describes 2 chronic inflammatory conditions that affect the intestines: Crohn's disease and ulcerative colitis. Crohn's disease is characterized by inflammation affecting any part of the gastrointestinal tract (from mouth to anus) and typically involves patches of inflammation between healthy segments of the small and large intestines. The inflammation is typically deep and can penetrate the walls of the intestine.[10] Ulcerative colitis involves more continuous segments of inflammation, typically in the colon, rectum, and anus. The inflammation is shallower, affecting only the inner lining of the intestines. People with severe cases of inflammatory bowel disease will likely need colorectal surgery to address complications such as bowel obstruction from scarring and fistulas.[10]

The prevalence of inflammatory bowel disease (including both Crohn's disease and ulcerative colitis) in Canada is estimated to be among the highest worldwide and is projected to increase from 0.82% of the general population (322,600 people) in 2023 to 1.08% (470,000 people) in 2035.[11]

Other Conditions

Other less common benign conditions that may require colorectal surgery include acute bowel obstruction and genetic conditions. One such genetic condition is familial adenomatous polyposis, which leads to the increased formation of polyps in the colon and can increase one's risk of developing colorectal cancer if the polyps are not prophylactically removed. Another is Lynch syndrome (hereditary nonpolyposis colorectal cancer), the most common cause of hereditary colorectal cancer,[12] arising from inherited changes in genes involved in DNA repair that predispose people with these genetic variants to developing cancer.[13]

The prevalence of familial adenomatous polyposis has been estimated in international registries to be 1 in 100,000,[14] and the prevalence of Lynch syndrome in US, Canadian, and Australian populations is estimated to be 1 in 279.[12]

Standard Approaches to Assessing Perfusion

The standard approaches that surgeons use to assess perfusion during colorectal surgery involve a visual assessment of the planned resection area. Various techniques may be used, including the following:

- Assessing the colour of the bowel (under white light, pink indicates well-perfused tissue)
- Feeling a palpable pulse in the mesentery
- Observing pulsatile arterial bleeding (i.e., assessing whether pulsatile bleeding is seen at the divided edge of the bowel or the marginal artery [the blood vessel closest to and parallel with the wall of the intestine])
- Technologies such as a Woods lamp, Doppler ultrasound, flowmetry, tonometry, or spectroscopy are also considered methods of visual assessment,[15] though they are not widely used in routine practice

Health Technology Under Review

Indocyanine green fluorescence imaging (ICGFI) is a technology that involves the use of a near-infrared imaging system to visualize real-time perfusion intraoperatively using a dye called indocyanine green (ICG), which binds strongly to plasma proteins.[16] During open or laparoscopic surgery, ICG is injected into the patient's bloodstream intravenously, and the imaging system uses a specialized light source to excite the dye, causing it to emit fluorescence that can be visualized on the display of the imaging system in real time. This form of tissue perfusion visualization involves no ionizing radiation, and ICG has a very short half-life, allowing surgeons to perform multiple intraoperative perfusion assessments throughout the surgery, if required. Contraindications for the use of ICG include iodine allergy and liver dysfunction, as the dye is cleared hepatically.

Stryker Canada (previously Novadaq Technologies) has developed 3 ICGFI systems, which have wide-ranging applications and can be used in gastrointestinal surgeries, breast reconstructions, neurosurgeries, reconstructive surgeries, and sentinel lymph node mapping (Stryker Canada, email communication, November 7, 2023). Several other imaging systems are also known to have ICGFI capabilities, including the da Vinci XI Surgical System (Intuitive Surgical) and the Rubina imaging systems (Karl Storz), but it is unclear how widely they are used in Ontario for perfusion assessment during colorectal surgery (Stryker Canada, email communication November 7, 2023).

It is anticipated that most new imaging systems being developed will have ICGFI capabilities, meaning that more hospitals will have access to this technology over time as they upgrade their imaging systems.

Regulatory Information

Health Canada has licensed several of Stryker Canada's near-infrared imaging systems, the da Vinci XI Surgical System, and the IMAGE1 S Rubina 4K imaging system. Stryker Canada's ICG dye product and another from Diagnostic Green also hold Health Canada licences. Tables 1a and 1b list the near-infrared imaging systems and ICG dyes currently licensed by Health Canada that may be used for colorectal surgery.

Table 1a: Near-Infrared Imaging Systems Licensed by Health Canada

Imaging system (manufacturer)	Surgical Approach	Device class	Licence number
Spy Portable Handheld Imaging System (SPY-PHI) with Spy-QP fluorescence assessment software (Novadaq Technologies[a])	Open	II	99155
1688 4K camera system with advanced imaging modalities (Stryker Endoscopy, a division of Stryker Corp. DBA Stryker Endoscopy)	Laparoscopic	II	104453
1788 4K camera system with advanced imaging modalities (Stryker Endoscopy, a division of Stryker Corp. DBA Stryker Endoscopy)	Laparoscopic	II	109261
IMAGE1 S Rubina 4K imaging system with NIR/ICG and 3D visualization (Karl Storz SE & Co. KG)	Laparoscopic	II	65128
Da Vinci XI Surgical System (Intuitive Surgical Inc.)	Robotic-assisted	IV	97378
Near-Infrared Fluorescence Imaging System (Spy Elite System)[b] (Novadaq Technologies[a])	Open	II	86199
Pinpoint Endoscopic Fluorescence Imaging System[b] (Novadaq Technologies[a])	Laparoscopic	II	81491

Abbreviations: ICG, indocyanine green; NIR, near-infrared.

[a]Novadaq Technologies Inc. was acquired by Stryker in 2017.

[b]This is an earlier version of a system that may still be used by some hospitals.

Source: Medical Devices Active Licence Listing database, 2024.[17]

Table 1b: ICG Dye Products Licensed by Health Canada

ICG Product (manufacturer)	Relevant use information	Drug identification number
Spy Agent Green (Novadaq Technologies ULC[a])	IV injection	02483653
Spy Agent Green (Novadaq Technologies ULC[a])	Kit for SPY-PHI	02498677
Spy Agent Green (Novadaq Technologies ULC[a])	Kit for SPY Elite	02483661
Spy Agent Green (Novadaq Technologies ULC[a])	Kit for AIM system	02483688
Spy Agent Green (Novadaq Technologies ULC[a])	Kit for Pinpoint system	02527839
ICG dye (Diagnostic Green Ltd)	–	02485796

Abbreviations: AIM, advanced imaging modality; ICG, indocyanine green; IV, intravenous.

Source: Drug Product Database, 2024.[18]

Ontario, Canadian, and International Context

Ontario

In Ontario, the use of ICGFI to assess anastomotic perfusion during colorectal surgery has been expanding in hospitals with access to upgraded imaging systems with ICG visualization capabilities. The costs of near-infrared imaging systems and ICG dye are currently funded through hospitals' global budgets, and there are currently no fee codes for the use of ICGFI. As advised by clinical experts and others with whom we consulted, as of the time of writing, we are aware of the use of ICGFI in colorectal surgeries in several hospitals, most of which are in urban centres.

The use of ICGFI in colorectal surgery at these sites is left to the discretion of the surgeon. Based on our consultations with colorectal surgeons and surgical oncologists, we learned that some use ICGFI selectively (i.e., based on the presence of risk factors and the treating surgeon's clinical judgment) because of the costs associated with the technology, whereas others use ICGFI for all their colorectal surgeries.

Given the broad indications for ICGFI, we were advised by the manufacturer of the SPY-PHI system that the system is being used in Ontario to assess tissue perfusion and blood flow or vascularity in a variety of surgical procedures including plastics reconstructive surgery, hepatobiliary surgery for open liver resections, transplant surgeries, coronary bypass, renal cancer surgeries, vascular surgeries, cardiac surgeries, and endocrine surgeries (Stryker Canada, email communication, November 7, 2023). The minimally invasive SPY imaging systems (1688 and 1788) are currently available in Ontario and are used primarily for laparoscopic procedures such as cholecystectomy, hernia repair, appendectomy, pelvic lymph node detection, hysterectomy, anterior cruciate ligament reconstruction, and knee and small joint arthroscopy (Stryker Canada, email communication, November 7, 2023).

Canada

In 2017, based on a health technology assessment of the use of ICGFI in colorectal surgery in British Columbia,[19] the British Columbia Health Technology Assessment Committee proposed that the technology be adopted in select hospitals under a controlled trial or monitored environment to confirm the cost-effectiveness parameters modelled in the health technology assessment.[20] However, it is unclear how widely the technology is being used in British Columbia now.

Through our expert consultations, we learned that at the time of writing, ICGFI is being used for colorectal surgery in a few other provinces (e.g., Alberta, Quebec, Nova Scotia); however, the total number of hospitals and the extent of use (i.e., all vs. selective cases) is unknown.

International

The European Association of Endoscopic Surgery (EAES) has published evidence-based consensus guidelines on the use of ICGFI in various surgical specialties, including colorectal surgery, given the rapid increase in its uptake across various clinical settings.[21] Based on the findings of their systematic review and meta-analysis, EAES issued a strong recommendation to use ICG fluorescence in colorectal surgery to assess tissue perfusion in order to reduce the risk of anastomotic leak.

The American Society of Colorectal Surgeons clinical practice guidelines for rectal cancer do not provide specific recommendations for assessing tissue perfusion but mention ICGFI as an option.[22]

While not formally recommended in any American guidelines yet, ICGFI is widely used in the United States to assess anastomotic perfusion in colorectal surgery. Clinical experts noted that ICGFI is becoming the standard of care in the United States because of the severity of risk posed by anastomotic leaks and the associated financial and possible medicolegal implications.

Equity Context

We use the PROGRESS-Plus framework to help explicitly consider health equity in our health technology assessments. PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist.[23] These characteristics include place of

residence; race or ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics (e.g., age) that stratify health opportunities and outcomes.[23]

Expert Consultation

We engaged with experts in the specialty areas of colorectal surgery and surgical oncology, as well as others with expertise in the use of ICGFI, to help inform the development and refinement of the research questions, review methods, and review results, as well as to contextualize the evidence on ICGFI for colorectal surgery to Ontario.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42024515923), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What is the effectiveness of indocyanine green fluorescence imaging (ICGFI) compared with visual assessment alone for the visualization of anastomotic perfusion during colorectal surgery?

Methods

Clinical Literature Search

We performed a clinical literature search on January 29, 2024, to retrieve studies published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[24]

We created database auto-alerts in MEDLINE and Embase, and monitored them until September 4, 2024. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Randomized controlled trials (RCTs) and comparative observational cohort studies (with a contemporaneous control group)

Exclusion Criteria

- Animal and in vitro studies
- Noncomparative observational studies, case-control studies, cross-sectional studies, nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries

Participants

Inclusion Criteria

- Adults (aged 18 years and older) undergoing colorectal surgery requiring the creation of an anastomosis for malignant or benign conditions, including colorectal cancer, diverticulitis, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), and bowel obstruction

Exclusion Criteria

- Individuals undergoing colorectal surgery that does not involve the creation of an anastomosis in the colon

Intervention

Inclusion Criteria

- Use of ICGFI to visualize anastomotic perfusion

Exclusion Criteria

- Use of other methods or technologies to visualize anastomotic perfusion
- Use of ICGFI for other purposes (e.g., sentinel node biopsy)

Comparators

Inclusion Criteria

- Visual assessment alone to assess anastomotic perfusion, specifically:
  - Assessing perfusion under white light based on the colour of the tissue (pink indicating well-perfused tissue)
  - Palpable pulse in mesentery
  - Pulsatile arterial bleeding (i.e., assessing perfusion based on whether pulsatile bleeding is seen at the divided edge of the bowel or the marginal vessel)
  - Use of technologies such as a Woods lamp, Doppler ultrasound, flowmetry, tonometry, or spectroscopy

Exclusion Criteria

- Any alternative methods or technologies used to assess anastomotic perfusion that are not based on visual assessment alone

Outcome Measures

- All postsurgical outcomes within 90 days after surgery:
  - Anastomotic leak (AL)
  - Readmission
  - Reoperation
  - Sepsis
  - Length of hospital stay
  - Mortality
  - Quality of life

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria. A single reviewer then screened all remaining citations using Covidence[25] and obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

One reviewer extracted relevant data on study characteristics, risk-of-bias items, and PICOTS elements (i.e., population, intervention, comparator, outcome, time, and setting) using a data form.

We contacted study authors to request clarification on the published analysis as needed.

Equity Considerations

Potential health inequities related to the use of ICGFI for colorectal surgery were not evident during scoping. However, our clinical experts noted that greater access to ICGFI may be available in hospitals with more resources (e.g., those with higher donor support). We were unable to report on PROGRESS-PLUS participant characteristics as this information was not reported in any of the included studies.

Statistical Analysis

One reviewer assessed for the presence and extent of clinical, methodological, and statistical heterogeneity across studies when interpreting the results.[26] Where outcome data between studies were available and it was appropriate to do so, we performed a random-effects meta-analysis using the web-based version of RevMan.[27]

A tabular or narrative summary of results is provided where meta-analysis was not appropriate and for subgroups for which data were available. No data were available to investigate AL with and without ICGFI by smoking status, American Society of Anesthesiologists Physical Status Classification System score (ASA score; used to assess perioperative risk), or surgery duration.

Critical Appraisal of Evidence

One reviewer assessed the risk of bias using the Cochrane Risk-of-Bias Tool[28] for RCTs and the Risk-of-Bias Assessment Tool for Nonrandomized Studies (RoBANS)[29] for comparative observational cohort studies (Appendix 2). We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[30]

Results

Clinical Literature Search

The clinical literature search yielded 804 citations, including grey literature results and the removal of duplicates, published between database inception and January 29, 2024. We identified 1 additional eligible study from database alerts (monitored until September 4, 2024).

We examined 32 systematic reviews that had some overlap with our research question but not enough to leverage in this review. We found that none were sufficiently up to date (i.e., they were missing recently published RCTs) and that the studies varied in terms of population (both indication and location of colorectal surgery) and study designs included. However, we scanned the reference lists of all identified reviews to confirm that no relevant studies were missed.

In total, we included 19 studies[31-49] (6 RCTs and 13 comparative nonrandomized studies). See Appendix 3 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical systematic review.

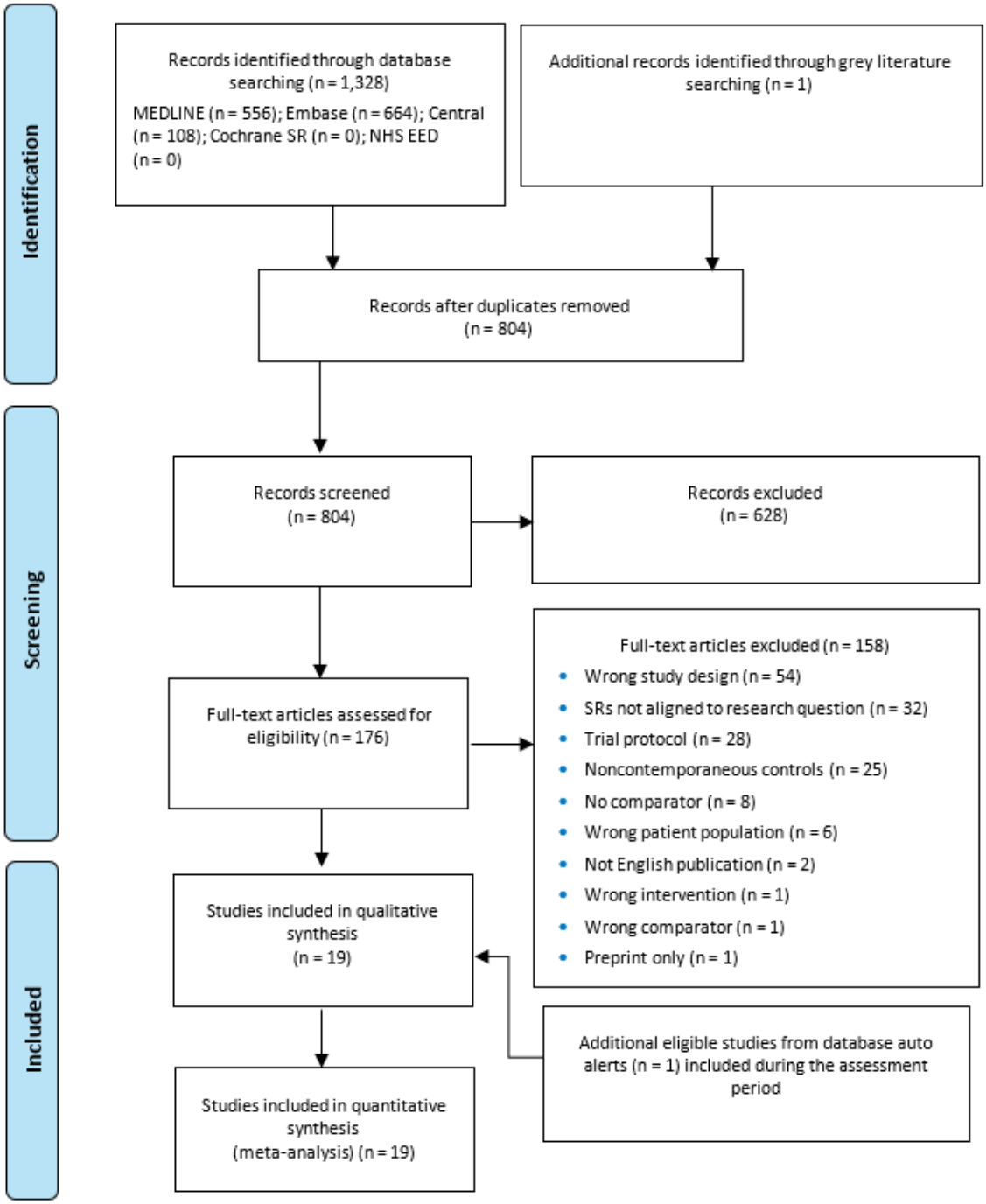

Figure 1: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical systematic review. The clinical literature search yielded 804 citations, including grey literature searches and after removing duplicates, published between database inception and January 29, 2024. We screened the abstracts of the 804 identified studies and excluded 628. We assessed the full text of 176 articles and excluded a further 158. One additional eligible study was identified from database auto alerts during the assessment period. In the end, we included 19 articles in the quantitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SR, systematic review.
Source: Adapted from Page et al.[50]

Characteristics of Included Studies

The included studies were conducted in various locations internationally including China, Germany, Hong Kong, Italy, Japan, Mexico, the Netherlands, Poland, Russia, Spain, the United Kingdom, and the United States. Five were multicentre studies,[32,34,36,47-49] while all others were conducted at a single site. No studies reported information on study participants' ethnicity, race, culture or language, place of residence, gender identity, disability, occupation or employment, education, or socioeconomic status. No studies evaluated quality of life as an outcome.

Table 2 summarizes the characteristics of the included studies. Across studies, ICG dose varied, as did the near-infrared imaging systems used. Perfusion assessment in the control groups varied but involved white light visualization or other typical methods of assessment. However, several studies did not describe in detail the control perfusion assessment.[37,39,40,42,43,46,47] All studies reported that no adverse reactions or events related to the ICG dye occurred.

About half the included studies reported no statistically significant differences in clinical or demographic characteristics between the ICGFI and control groups.[33-37,41,42,44,45] The other studies reported differences in participant characteristics, comorbidities, or prognostic factors at baseline between the study groups. Specifically:

- Jafari et al[31] reported that obesity (44% vs. 27 %), hyperlipidemia (13% vs. 9 %), and cardiac disease (19% vs. 9%) were more prevalent in the ICGFI group than in the control group. Diabetes mellitus (18% vs. 0 %), pulmonary disease (23% vs. 6 %), and history of smoking (27% vs. 13%) were more prevalent in the control group than in the ICGFI group (*P* values not reported).
- In the PILLAR III RCT,[32] the authors reported that patient demographics and comorbidities, including male sex, obesity, peripheral vascular disease, and malnutrition, were similar between the 2 groups, as were preoperative vitals and laboratory measures. However, there were statistically significantly more smokers in the ICGFI group than in the control group ($P < .05$).
- Tueme-de la Peña et al[46] reported a statistically significantly higher number of lymphocytes among participants in the ICGFI group versus the control group ($P < .05$) but no other statistically significant differences between groups in terms of clinical or demographic characteristics.
- Marquardt et al[41] noted that among participants undergoing right hemicolectomy, there were statistically significantly more ASA III and IV patients in the control group versus the ICGFI group. There were no statistically significant differences between groups among participants undergoing rectal resection.
- Starker and Chinn[43] reported statistically significant differences between the ICGFI and control groups with more blood transfusions, diverting ileostomies, cancer, and laparoscopic procedures in the ICGFI group ($P < .05$).

Table 2: Characteristics of Studies Included in the Clinical Systematic Review

						Interventions		ICGFI		Control	
Author/trial name, year	**Country**	**Study type (n, sites)**	**Indication(s)**	**Surgical approach(es), procedure(s)**	**Outcomes of interest reported**	**ICG dose (manufacturer, location), NIR system (manufacturer, location)**	**Comparator**	**N, % male**	**Age, y**	**N, % male**	**Age, y**
AVOID trial, 2024[49]	The Netherlands	RCT (8)	Malignant or benign conditions	Laparoscopic, robotic-assisted Ileocecal resection, R hemicolect-omy, travers-ectomy, L hemi-colectomy, sigmoid-ectomy, LAR, subtotal colectomy, ta-TME (elective)	AL (grades B or C, ISREC) within 90 d, mortality (AL-related and all-cause) within 30 d and 90 d, LOS, readmission within 90 d (AL-related and all-cause)	5 mg IV ICG (Verdye, Diagnostic Green, Germany) Visera Elite II (Olympus, the Netherlands) or da Vinci Firefly (Intuitive Surgical, United States)	Conventional methods such as visual assessment of tissue color, palpation of mesenteric arteries	463 (54)	MD: 69.0 (IQR: 59–75)	468 (50)	MD: 67.5 (IQR: 59–76)
De Nardi et al, 2020[34]	Italy	RCT[a] (3)	Malignant or benign conditions	Laparoscopic LAR, LC (all referred patients)	AL within 30 d, readmission, reoperation, sepsis, LOS, mortality	0.3 mg/kg IV ICG (Pulsion Medical, Germany) NIR system not specified (Karl Storz, Germany)	Visual assessment, active bleeding of marginal artery and bowel edge, pulsatile flow, pink color	118 (50.8)	MN: 6.1	122 (54.1)	MN: 65.1
EssentiAL trial, 2023[36]	Japan	RCT (41)	Rectal cancer	Laparoscopic, robotic-assisted, transanal ISR, HAR, LAR, ta-TME (elective)	AL (grades A, B, C), AL (grades B, C), reoperation, LOS	12.5 mg IV ICG (Diagnogreen, Japan) 1588 or 1688 (Stryker, United States)	Active bleeding from resection margin, palpable pulse in mesentery, lack of discolouration at surgeon's discretion	mITT: 422 (63)	MD: 66 (range: 56–73)	mITT: 417 (65.7)	MD: 67 (range: 58–74)

						Interventions		ICGFI		Control	
Author/trial name, year	**Country**	**Study type (n, sites)**	**Indication(s)**	**Surgical approach(es), procedure(s)**	**Outcomes of interest reported**	**ICG dose (manufacturer, location), NIR system (manufacturer, location)**	**Comparator**	**N, % male**	**Age, y**	**N, % male**	**Age, y**
FLAG trial, 2020[33]	Russia	RCT (1)	Malignant or benign sigmoid or rectal neoplasm	Open, laparoscopic LAR with TME, AR, LC (elective)	AL within 30 d, reoperation, LOS, mortality	0.2 mg/kg IV ICG (Pulsion Medical, Germany) D-Light P SCB (Karl Storz, Germany)	Visual assessment of blood perfusion	187 (49.2)	MD: 63 (range: 21–86)	190 (48.4)	MD: 63 (range: 66–85)
Gach et al, 2023[35]	Poland	RCT[b] (1)	Rectal cancer	Laparoscopic LAR with TME or partial ME (elective)	AL within 14 d, reoperation, LOS, mortality	ICG dose NR (Verdye, Diagnostic Green, Germany) NIR system NR	Visible light	41 (63.4)	MN: 64.7 (SD: 10.6)	35 (60.0)	64.8 (SD: 10.6)
PILLAR III trial, 2021[32]	United States	RCT (25)	Rectal or rectosigmoid neoplasm	Open, laparoscopic, robotic-assisted LAR (elective)	AL	3.0 (± 1.0) mL of 2.5 mg/mL concentration IV ICG PINPOINT or SPY Elite (Stryker, United States)	Surgeon's standard practice (not described)	178[c](61.2); 175 included	MN: 57.2 (SD: 11.4)	169[c] (58.6); 168 included	MN: 57.0 (SD: 11.4)
Brescia et al, 2018[37]	Italy	Nonrandomized retrospective (1)	Colon cancers (right, left, transverse, splenic flexure, hepatic flexure), rectal cancers, diverticular disease	Laparoscopic Procedures NR (elective)	AL, LOS, readmission, mortality, complications	0.25 mg/kg IV ICG-Pulsion (Pulsion Medical Systems, Germany) SPIES (Karl Storz, Germany)	Not described	75 (57.3)	MN: 37.1 (SD: 6)	107 (58.9)	MN: 65.7 (SD: 7)

						Interventions		ICGFI		Control	
Author/trial name, year	**Country**	**Study type (n, sites)**	**Indication(s)**	**Surgical approach(es), procedure(s)**	**Outcomes of interest reported**	**ICG dose (manufacturer, location), NIR system (manufacturer, location)**	**Comparator**	**N, % male**	**Age, y**	**N, % male**	**Age, y**
Chen et al, 2023[38]	China	Nonrandomized retrospective (1)	Rectal cancer	Laparoscopic-assisted transanal Ta-TME (elective)	AL within 30 d	0.25 mg/kg IV ICG (NR) D-Light P (Karl Storz, Germany) or 1588 AIM (Stryker, United States)	White light	143 (51.0)	MD: 69 (range: 41–90)	143[d] (49.7)[d]	MD: 67[d] (range: 40–88)[d]
Flores-Rodriguez et al, 2023[39]	Spain	Nonrandomized retrospective (1)	Malignant or benign conditions	Open, minimally invasive LC, RC, rectal resection (elective)	AL, reoperation	0.3 mg/kg IV ICG (NR) NIR system NR	Not described	280 or 279 (61.1)	MN: 70.5 (SD NR)	505 (59.2)	71.7 (SD NR)
Freund et al, 2021[40]	United States	Nonrandomized retrospective (1)	Crohn's disease	Open, laparoscopic Redo ileocolic resection (elective)	AL, reoperation, readmission, LOS, mortality	3.5 mL IV ICG (NR) PINPOINT (Stryker, United States)	Not described	12 (41)	MD: 53.5 (range: 23–77)	24 (54.1)	MD: 58 (range: 32–78)
Jafari et al, 2013[31]	United States	Nonrandomized retrospective (1)	Rectal cancer	Robotic-assisted uLAR, LAR, ISR (elective)	AL within 60 d, reoperation, readmission	6-8 mg IV ICG (NR) da Vinci Si HD vision system, Firefly (Intuitive Surgical, United States); other NIR systems not specified (Olympus, Japan; Karl Storz, Germany; Stryker, United States; Novadaq, Canada)	White light	16 (75)	MN: 58 (SD NR)	22 (73)	MN: 63 (SD NR)

						Interventions		ICGFI		Control	
Author/trial name, year	**Country**	**Study type (n, sites)**	**Indication(s)**	**Surgical approach(es), procedure(s)**	**Outcomes of interest reported**	**ICG dose (manufacturer, location), NIR system (manufacturer, location)**	**Comparator**	**N, % male**	**Age, y**	**N, % male**	**Age, y**
Marquardt et al, 2020[41]	Germany	Nonrandomized retrospective (1)	Colorectal cancer, diverticulitis	Open, laparoscopic, robotic-assisted R hemi-colectomy with CME, LAR with TME (elective, emergency)	Anastomotic healing rate	0.1–0.2 mg/kg IV ICG (Verdye, Diagnostic Green, Germany) SPY (Novadaq, Canada) or Firefly (Intuitive Surgical, United States)	Assessed by surgeon using widely discussed visual criteria	LAR+T, ME: 67 (52.2) R hemicolectomy: 76 (40.8)	LAR+TME, MD: 69 (range: 57–76) R hemicolectomy, MD: 74 (range: 65–80)	LAR+TME: 59 (62.7) R hemicolectomy: 149 (50.3)	LAR+TME, MD: 71 (range: 60–78) R hemicolectomy: 77 (range: 69–82)
Neddermeyer et al, 2022[42]	Germany	Nonrandomized retrospective (1)	Colorectal cancer, benign conditions	Open, laparoscopic, robotic-assisted Sigmoid resection, TME (elective)	AL, LOS, in-hospital mortality	5 mL of 5 mg/mL IV ICG (Pulsion Medical Systems, Germany) PINPOINT (Novadaq, Canada)	Not described	70 (68.6)	MD: 66.5 (range: 34–88)	62 (62.9)	MD: 59.5 (range: 33–93)
Starker and Chinn, 2018[43]	United States	Nonrandomized retrospective (1)	Diverticular disease, cancer, polyps, Hartmann closure, other (IBD, prolapse, volvulus, colonic inertia)	Surgical approach not described Colectomy (various, NR)	AL within 30 d	Not described PINPOINT (Novadaq, Canada)	Not described	238 (52.9)	MN: 62.4 (SD NR)	109 (45.8)	MN: 60.8 (SD NR)

						Interventions		ICGFI		Control	
Author/trial name, year	**Country**	**Study type (n, sites)**	**Indication(s)**	**Surgical approach(es), procedure(s)**	**Outcomes of interest reported**	**ICG dose (manufacturer, location), NIR system (manufacturer, location)**	**Comparator**	**N, % male**	**Age, y**	**N, % male**	**Age, y**
Su et al, 2020[44]	China	Nonrandomized retrospective (1, with 1 surgeon)	Colon cancer	Laparoscopic RC, LC, TC	AL within 60 d	3 mL of 25 mg/ 10 mL IV ICG (Eisai, Japan) Opto-cam 2100 (OptoMedic, China)	Vision with naked eye	84 (57.1)	MN: 59.1 (SD: 11.1)	105 (52.4)	MN: 60.2 (SD: 9.8)
Tsang et al, 2020[45]	Hong Kong	Nonrandomized prospective (1)	Malignant or benign conditions	Open, laparoscopic, robotic-assisted Elective R hemi-colectomy, L hemi-colectomy, AR, LAR/TME (elective)	AL within 30 d, reoperation within 30 d, LOS	10 mg IV ICG (NR) Da Vinci Xi, Firefly (Intuitive Surgical, United States) OTV-S300 with IR light source, CLV-S200-IR (Olympus, Japan)	Surgical team assessment of serosal colour, palpable pulsations, visible peristalsis, active bleeding from cut bowel edges	62 (62.9)	MN: 69.8 (SD: 9.9)	69 (68.1)	MN: 67.7 (SD: 11.6)
Tueme-de la Peña et al, 2023[46]	Mexico	Nonrandomized retrospective (1)	Colon cancer, rectal cancer, metastatic gynecologic cancer, diverticular disease, colonic polyps, other diagnoses	Open, laparoscopic RC, LC, sigmoid colectomy, LAR, uLAR	AL, LOS	7.5 mg IV ICG (NR) 1688 (Stryker, United States)	Not described	83 (53)	MN: 58 (SD: 49–65)	85 (48.2)	MN: 61 (SD: 52.2–69.5)
Watanabe et al, 2020[47]	Japan	Nonrandomized retrospective (3)	Rectal cancer	Laparoscopic LAR (elective)	AL within 30 d, reoperation within 30 d, LOS	0.25 mg/kg IV ICG (NR) D-Light P (Karl Storz, Germany) 1588 AIM (Stryker, United States)	Not described	211[d] (60.7)[d]	MD: 66[d] (range: 34–92)[d]	211[d] (32.1)[d]	MD: 66[d] (range: 36–89)[d]

						Interventions		ICGFI		Control	
Author/trial name, year	**Country**	**Study type (n, sites)**	**Indication(s)**	**Surgical approach(es), procedure(s)**	**Outcomes of interest reported**	**ICG dose (manufacturer, location), NIR system (manufacturer, location)**	**Comparator**	**N, % male**	**Age, y**	**N, % male**	**Age, y**
Watanabe et al, 2021[48]	Japan	Nonrandomized retrospective (3)	Colon cancer	Open, laparoscopic, robotic-assisted Procedures NR (elective)	AL within 30 d, mortality within 30 d, reoperation, LOS	0.25 mg/kg IV ICG (NR) D-Light P (Karl Storz, Germany) 1588 AIM (Stryker, United States)	Pulsation of the mesenteric blood vessels, color change	370[d] (51.5)[d]	MD: 72 (IQR: 66–79)[d]	370[d] (51.5)[d]	MD: 72[d] (IQR: 66–79)[d]

Abbreviations: AL, anastomotic leak; AR, anterior resection; CME, complete mesocolic excision; HAR, high anterior rectal resection; IBD, inflammatory bowel disease; ICG, indocyanine green; IQR, interquartile range; ISR, intersphincteric resection; IV, intravenous; L, left; LAR, low anterior resection; LC, left colectomy; LOS, length of stay; MD, median; ME, mesorectal excision; mITT, modified intention-to-treat; MN, mean; NIR, near-infrared; NR, not reported; R, right; RC, right colectomy; RCT, randomized controlled trial; SD, standard deviation; ta, transanal; TC, transverse colectomy; TME, total mesorectal excision; uLAR, ultra low anterior resection.

[a]Superiority trial.

[b]Interim report.

[c]ITT population for the study. Ultimately, 175 and 168 participants were enrolled in the ICGFI and control groups, respectively.[32]

[d]After matching.

Risk of Bias in the Included Studies

Among the included RCTs, 3 were at low or unclear risk of bias with regard to randomization, allocation concealment, selective reporting, and other domains.[33,34,36] None of the RCTs were double-blind; however, the impact of this is unclear. Three RCTs were judged to be at high risk of bias in at least 1 domain: incomplete outcome data,[32] selective reporting,[49] and/or other domains.[32,35] Two of these studies had issues with inadequate numbers of participants: 1 related to stopping the trial early due to poor recruitment[32] and 1 related to the study being a preliminary analysis with less than half the planned sample size and no subsequently published analyses.[35]

Most of the nonrandomized comparative cohort studies were judged to be at low or unclear risk of bias with regard to participant selection and intervention measurement. None of the studies employed blinding of outcome assessors; however, its absence was judged as unlikely to affect outcome measurements. Only 5 of the nonrandomized studies employed matching between the intervention and control groups on known prognostic characteristics to account for confounding.[38-40,47,48] Two studies were judged to be at high risk of bias on 1 or more domains of potential bias: 1 study was judged to be at high risk of bias on consideration of confounders, missing outcome data, and selective outcome reporting,[31] and the other study was judged to be at high risk of bias because of incomplete outcome data owing to issues with participant numbers.[41]

Tables A1 and A2 (Appendix 2) provide our risk-of-bias assessments for the included RCTs and nonrandomized comparative studies, respectively.

Anastomotic Leak

All 19 studies reported the occurrence of AL after colorectal resection with ICGFI versus without.[31-49] The definition of AL in the studies that defined this outcome varied but typically encompassed symptomatic AL, clinically suspected AL (e.g., based on surgical drain output), or radiologically detected AL (e.g., visualized by contrast endoscopy or computerized tomography [CT]). Of note, Tsang et al[45] included perianastomotic abscesses in their definition of AL, and the AVOID trial[49] did not include radiologically detected AL or intra-abdominal abscesses unrelated to the anastomosis in its definition.

Most studies were designed to assess AL within 30 days[33,34,38,43,45,47,48] or 60 days[31,44] following surgery. In the AVOID trial,[49] the primary outcome was AL within 90 days, and the authors assessed AL within 30 days as a secondary outcome. Gach et al[35] defined a primary outcome of AL within 14 days. The time horizon used in the remaining studies was unclear.[32,36,37,39-42,46]

The pooled risk of AL was 42% lower with ICGFI than without (risk ratio [RR] 0.58, 95% confidence interval [CI] 0.47 to 0.72; Figure 2), corresponding to an absolute effect of 32 fewer ALs per 1,000 cases (from 40 fewer to 21 fewer). The estimate of relative effect was similar across RCTs and nonrandomized studies (test for subgroup effect, $P = .05$; Figure 2).

We rated the GRADE quality of evidence (GRADE) for this outcome as Low (nonrandomized studies; RCTs downgraded for imprecision and risk of bias; Appendix 2, Table A3).

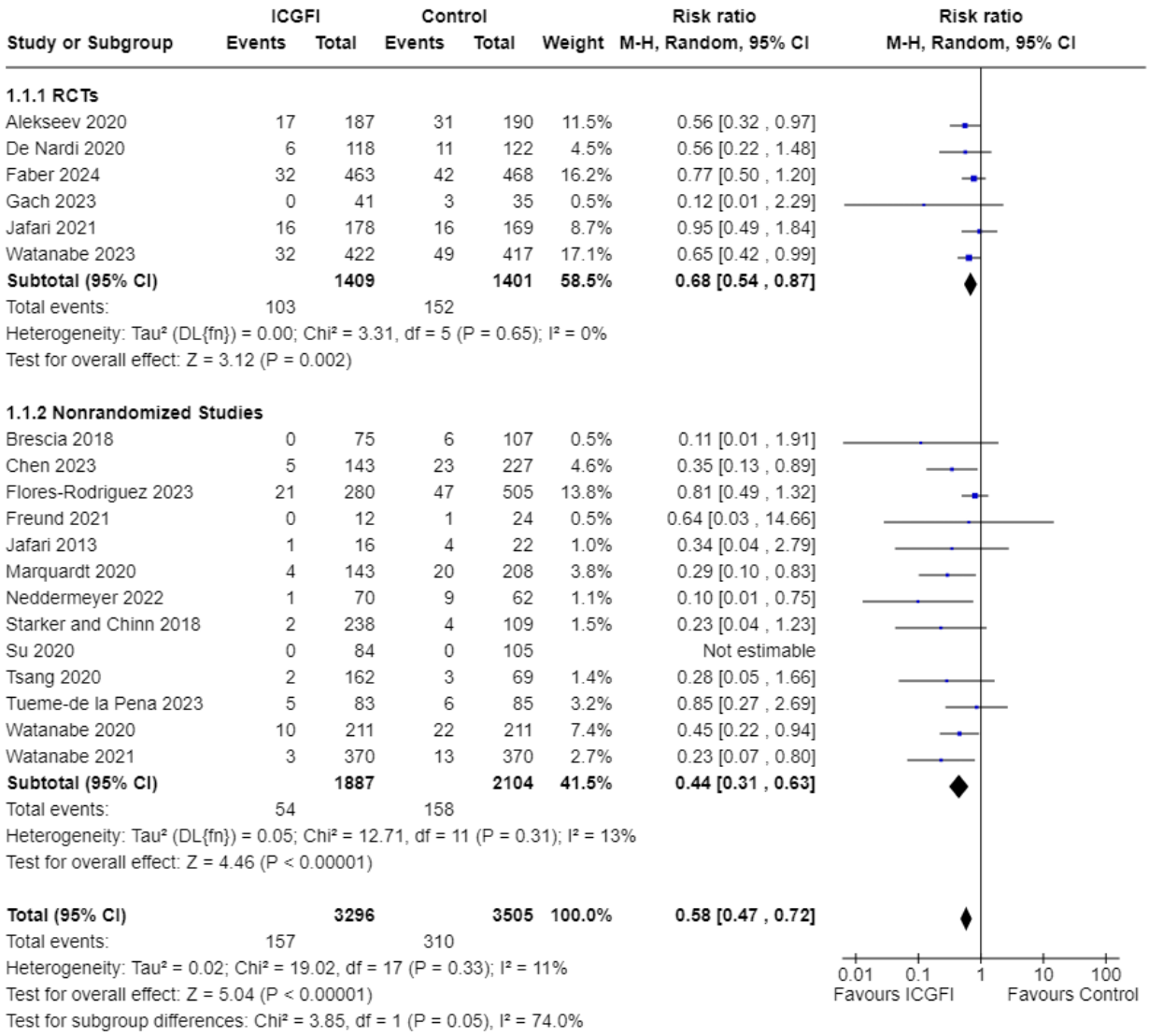

Figure 2: Anastomotic Leak Following Colorectal Resection, With ICGFI Versus Without

Abbreviations: CI, confidence interval; ICGFI, indocyanine green fluorescence imaging; M-H, Mantel-Haenzel; RCT, randomized controlled trial.

Given that the 90-day AL rate was the primary outcome for the AVOID trial, we included it in the meta-analysis (Figure 2).[49] However, the authors also reported that the 30-day AL rate was not statistically significantly different from the 90-day rate: 6% (30/463) in the ICGFI group versus 9% (40/468) in the control group (*P* = .23).

Subgroup Analyses

Anastomotic leak was the only outcome for which subgroup data were available. There were no data on AL with and without ICGFI by smoking status, ASA score, benign versus malignant indication, or duration of operation. The available subgroup data are presented below.

Anastomotic Leak by Location of Colorectal Resection

As shown in Table 3, there was variability in the reporting of AL with and without ICGFI by location of colon resection or anastomosis. Two studies reported AL by relative location of the anastomosis within the colon,[33,48] and 4 others reported AL by area of colon resected.[39,41,42,49] Some data suggest a trend toward a possible reduction of AL with ICGFI versus control in cases of left-sided resection or anastomosis lower in the colon.[33,42,48,49] Marquardt et al[41] were the only ones who planned to separate their results by surgical procedure; however, the authors provided no a priori subgroup hypothesis regarding the anticipated direction of effect.

Table 3: Anastomotic Leak by Location of Colorectal Resection, With ICGFI Versus Without

Author/trial name, year	Location of colon resection	ICGFI, n/N (%)	Control, n/N (%)	*P* value	Relative effect (95% CI)	*P* value
AVOID trial, 2024[49]	Right-sided colon resection (within 90 d)	8/189 (4)	9/208 (4)	.96	RR: 0.98 (0.39–2.48)	.96
AVOID trial, 2024[49]	Left-sided colon resection (within 90 d)	20/264 (8)	33/257 (13)	.047	RR: 0.59 (0.35–1.00)	.047
AVOID trial, 2024[49]	Transversectomy,subtotal colectomy (within 90 d)	4/10 (40)	0/3 (0)	.50	–	–
AVOID trial, 2024[49]	Rectosigmoid resection (within 90 d; post hoc analysis)	19/222 (4)	32/218 (15)	.045	RR: 0.58 (0.34–1.00)	.045
FLAG trial, 2020[33]	High anastomosis: 9–15 cm from anal verge	1/76 (1.3)	4/86 (4.6)	.37	OR: 0.27 (0.03–2.50)[a]	–
FLAG trial, 2020[33]	Low anastomosis: 4–8 cm from anal verge	16/111 (14.4)	27/104 (25.7)	.04	OR: 0.48 (0.24–0.96)[a]	–
Flores-Rodriguez et al, 2023[39]	L coletomy	5.4%[b]	9.6%[b]	–	OR: 1.86 (0.8–4.2)	.14
Flores-Rodriguez et al, 2023[39]	R colectomy	10.0%[b]	10.3%[b]	–	OR: 1.03 (0.4–2.4)	.95
Flores-Rodriguez et al, 2023[39]	Rectal resection	9.8%[b]	6.3%[b]	–	OR: 0.61 (0.2–2.2)	.46
Marquardt et al, 2020[41]	LAR	3/67 (4.5)	8/59 (13.6)	.068	OR: 0.30 (0.08–1.18)[a]	–
Marquardt et al, 2020[41]	R hemicolectomy + CME	1/76 (1.3)	12/149 (8.1)	.032	OR: 0.15 (0.02–1.19)[a]	–
Neddermeyer et al, 2022[42]	Sigmoid resection	0/38 (0)	4/32 (12.5)	.03922	OR: 0.08 (0.00–1.59)[a]	–
Neddermeyer et al, 2022[42]	TME	1/32 (3.1)	5/30 (16.7)	.09858	OR: 0.16 (0.02–1.47)[a]	–
Watanabe et al, 2021[48]	Ileocolic anastomosis	2/260 (0.8)	7/274 (2.6)	.109	OR: 0.30 (0.06–1.44)[a]	–
Watanabe et al, 2021[48]	Colocolonic anastomosis	1/110 (0.1)	6/96 (6.3)	.035	OR: 0.14 (0.02–1.12)[a]	–

Abbreviations: CI, confidence interval; CME, complete mesocolic excision; ICGFI, indocyanine green fluorescence imaging; L, left; LAR, low anterior resection; OR, odds ratio; R, right; RR, risk ratio; TME, total mesorectal excision.

[a]Odds ratio calculated from data reported in the article.

[b]Unable to calculate n/N for each procedure because the authors did not report in which group(s) the deaths occurred.[39]

Anastomotic Leak by Severity of Leak

Eight studies reported AL severity (Table 4).[33,34,36,38,41,42,47,49] Most studies[33-36,38,41,42,49] classified AL severity according to the International Study Group of Rectal Cancer (ISREC) system, which grades AL severity based on the need for intervention: asymptomatic and no active intervention required (grade A), symptomatic and active intervention required but manageable without relaparotomy (grade B), or symptomatic and relaparotomy required (grade C).[51] Watanabe et al (2020)[47] categorized AL severity using the Clavien-Dindo grading system, which also classifies AL on the basis of the medical consequences and treatment required.[52,53]

Given that both ISREC and Clavien-Dindo are accepted severity classification systems for colorectal AL,[54] Table 4 presents the subgroup data for AL severity as reported by the study authors. It is unclear whether ICGFI has more of an impact on one severity of AL over another.

Table 4: Anastomotic Leak by Severity, With ICGFI Versus Without

Author/trial name, year	AL grade	ICGFI, n/N (%)	Control, n/N (%)	*P* value	Risk ratio (95% CI)	*P* value
Chen et al, 2023[38]	ISREC grade A	4/143 (2.8)	12/143 (8.4)	.040	0.33 (0.11–1.01)[a]	–
De Nardi et al, 2020[34]	ISREC grade A	0/118 (0)	1/122 (0.8)	ns	0.34 (0.01–8.37)[a]	–
FLAG trial, 2020[33]	ISREC grade A	7/187 (3.7)	21/190 (11)	.01	0.34 (0.15–0.78)[a]	–
Marquardt et al, 2020[41]	ISREC grade A, total	1/143 (0.7)	1/208 (0.5)	NR	1.45 (0.06–23.06)[a]	–
Neddermeyer et al, 2022[42]	ISREC grade A	0/70 (0)	0/62 (0)	nc	NE	–
Chen et al, 2023[38]	ISREC grade B	1/143 (0.7)	10/143 (7.0)	.006	0.10 (0.01–0.77)[a]	–
De Nardi et al, 2020[34]	ISREC grade B	2/118 (1.7)	3/122 (2.5)	ns	0.69 (0.12–4.05)[a]	–
FLAG trial, 2020[33]	ISREC grade B	6/187 (3.2)	7/190 (3.7)	1.0	0.87 (0.30–2.54)[a]	–
Marquardt et al, 2020[41]	ISREC grade B, LAR only	0/67 (0)	1/59 (1.7)	NR	–	–
Marquardt et al, 2020[41]	ISREC grade B, R hemicolectomy only	0/76 (0)	0/149 (0)	NR	–	
Marquardt et al, 2020[41]	ISREC grade B, total	0/143 (0)	1/208 (0.5)	NR	0.48 (0.02–11.79)[a]	
Neddermeyer et al, 2022[42]	ISREC grade B	0/70 (0)	1/62 (1.6)	nc	0.30 (0.01–7.13)[a]	–
Chen et al, 2023[38]	ISREC grade C	0/143 (0)	1/143 (0.7)	1.00	0.33 (0.01–8.11)[a]	–
De Nardi et al, 2020[34]	ISREC grade C	4/118 (3.4)	7/122 (5.7)	ns	0.59 (0.18–1.97)[a]	–
FLAG trial, 2020[33]	ISREC grade C	4/187 (2.1)	3/190 (1.6)	.72	1.35 (0.31–5.97)[a]	–

Author/trial name, year	AL grade	ICGFI, n/N (%)	Control, n/N (%)	*P* value	Risk ratio (95% CI)	*P* value
Marquardt et al, 2020[41]	ISREC grade C, LAR only	2/67 (3.0)	6/59 (10.2)	NR	–	–
Marquardt et al, 2020[41]	ISREC grade C, R hemicolectomy only	1/76 (1.3)	12/149 (8.1)	NR	–	–
Marquardt et al, 2020[41]	ISREC grade C, total	3/143 (2.1)	18/208 (8.7)	NR	0.24 (0.07–0.81)[a]	–
Neddermeyer et al, 2022[42]	ISREC grade C	1/70 (1.4)	8/62 (12.9)	.007459	0.11 (0.01–0.86)[a]	–
Watanabe et al, 2020[47]	Clavien-Dindo grade ≥ III	6/211 (2.8)	20/211 (9.5)	.007	0.30 (0.12–0.73)[a]	–
AVOID trial, 2024[49]	ISREC grades B + C, 90 d	32/463 (7)	42/468 (9)	.24	0.77 (0.50–1.20)	.24
AVOID trial, 2024[49]	ISREC grades B + C, 30 d	30/463 (6)	40/468 (9)	.23	0.76 (0.48– 1.20)[a]	–
EssentiAL trial, 2023[36]	ISREC grades B + C	20 (4.7)	34 (8.2)	.044	0.581 (0.34–0.993)	.044
Watanabe et al, 2020[47]	Clavien-Dindo grades ≥ II	10/211 (4.7)	22/211 (10.4)	.042	0.45 (0.22–0.94)[a]	–

Abbreviations: AL, anastomotic leak; CI, confidence interval; ICGFI, indocyanine green fluorescence imaging; ISREC, International Study Group of Rectal Cancer; L, left; LAR, low anterior resection; nc, not calculable; NE, not estimable; NR, not reported; ns, not statistically significant; R, right; RR, risk ratio; TME, total mesorectal excision.

[a]Risk ratio calculated from subgroup data reported in the article.

Anastomotic Leak by Age

One study explored the occurrence of AL with ICGFI versus without between age groups. The authors of the EssentiAL trial[36] conducted a post hoc subgroup analysis of the odds of AL occurring among older versus younger study participants. However, it is unclear whether these groups were split at age 70 years (i.e., < 70 vs. > 70) or 75 years (i.e., < 75 vs. > 75) because both labels appear in the study protocol and in the results section of the publication. We emailed the authors for clarification but did not receive a response. Nonetheless, the authors reported that there was no statistically significant difference between age groups.

Anastomotic Leak by Surgical Approach

Seven studies used a single surgical approach: laparoscopic,[34,35,37,44,47] robotic-assisted,[31] or transanal.[38]

In addition, the authors of the EssentiAL trial[36] conducted within-study, post hoc comparisons of the odds of AL occurring between the ICGFI and control groups among their subgroups of participants undergoing laparoscopic surgery, robotic-assisted surgery, or transanal total mesorectal excision. They found no statistically significant differences in AL between the ICGFI and control groups by surgical approach.

Table 5 presents the data reported by study authors for AL with and without ICGFI by surgical approach.

Table 5: Anastomotic Leak by Surgical Approach, With ICGFI Versus Without

Author, year	Surgical approach	ICGFI, n/N (%)	Control, n/N (%)	*P* value	Odds ratio (95% CI)
DeNardi et al, 2020[34]	Laparoscopic	6/118 (5)	11/122 (9)	.20	–
EssentiAL trial, 2023[36,a]	Laparoscopic	16/184 (8.7)	27/190 (14.2)	–	0.575 (0.299–1.107)[a]
Gach et al, 2023[35]	Laparoscopic	0/41 (0)	3/35 (8.6)	.093	–
Brescia et al, 2018[37]	Laparoscopic	0/75 (0)	6/107 (5.6)	.03	–
Su et al, 2020[44]	Laparoscopic	0/84 (0)	0/105 (0)		–
Watanabe et al, 2020[47]	Laparoscopic, Clavien-Dindo grade ≥ II	10/211 (4.7)	22/211 (10.4)	.042	–
Watanabe et al, 2020[47]	Laparoscopic, Clavien-Dindo grade ≥ III	6/211 (2.8)	20/211 (9.5)	.007	–
EssentiAL trial, 2023[36,a]	Robotic-assisted	14/202 (6.9)	19/184 (10.3)	–	0.647 (0.314–1.330)[a]
Jafari et al, 2013[31]	Robotic-assisted	1/16[b] (6)	4/22[b] (18)	NR	–
Chen et al, 2023[38]	Transanal TME	5/143 (3.5)	23/143 (16.1)	< .001	–
EssentiAL trial, 2023[36,a]	Transanal TME	2/36 (5.6)	3/43 (7.0)	–	0.784 (0.124–4.972)[a]

Abbreviations: CI, confidence interval; ICGFI, indocyanine green fluorescence imaging; NR, not reported; TME, total mesorectal excision.
[a]Post hoc within-study subgroup analysis comparing surgical approaches.[36]
[b]n estimated from back-calculation (rounded to the nearest whole number) from percentages reported in Jafari et al.[31]

Anastomotic Leak by Sex

The authors of the EssentiAL trial[36] conducted a within-study, post-hoc analysis of the odds of AL occurring in the ICGFI and control groups by sex and found no statistically significant difference (Table 6).

Table 6: Anastomotic Leak by Sex, With ICGFI Versus Without

Sex	ICGFI, n/N	Control, n/N	Odds ratio (95% CI)
Male	25/266	37/274	0.665 (0.388–1.138)
Female	7/156	12/143	0.513 (0.196–1.341)

Abbreviations: CI, confidence interval; ICGFI, indocyanine green fluorescence imaging.
Source: EssentiAL trial, 2023.[36]

Readmission

One RCT[49] and 4 nonrandomized studies reported readmission (Table 7).[37,38,40,44] However, no studies reported reasons for readmission (i.e., whether for AL or other indications). One study found statistically significantly fewer readmissions in the ICGFI group compared to control (0.7% vs. 7.7%, *P* = .003),[38] but 3 studies found no statistically significant difference between groups.[37,40,49] There were no readmissions in either group in the fourth nonrandomized study.[44]

We rated the certainty of the body of evidence for this outcome as Low (nonrandomized studies; RCTs, downgraded for imprecision and risk of bias; Appendix 2, Table A3).

Table 7: Readmission Following Colorectal Resection, With ICGFI Versus Without

Author/trial name, year	ICGFI, n/N (%)	Control, n/N (%)	Details, if provided	*P* value
AVOID trial, 2024[49]	59/463 (13)	63/468 (13)	90-d readmissions due to postoperative complications	.74
AVOID trial, 2024[49]	41/463 (9)	51/468 (11)	30-d readmissions due to postoperative complications	.30
Brescia et al, 2018[37]	0/75 (0)	3/107 (2.8)	–	ns[a]
Chen et al, 2023[38]	1/143 (0.7)	11/143 (7.7)	–	.003
Freund et al, 2021[40]	2/12 (16.6)	5/24 (20.8)	30-d readmission rate 2 in control group readmitted for percutaneous drainage of abdominal abscess	.99
Su et al, 2020[44]	0/84 (0)	0/105 (0)	–	NE

Abbreviations: ICGFI, indocyanine green fluorescence imaging; NE, not estimable; ns, not statistically significant.
[a]*P* value not reported.

The RCT by De Nardi et al[34] reported that 10 participants were readmitted for persistent fever or AL but did not provide information by treatment group. Jafari et al[31] stated in their methods that readmission was analyzed, but this outcome was not reported.

Reoperation

Thirteen studies reported reoperation.[31,33-38,40,42,44,45,47,48] Reoperation was combined with nonsurgical reintervention in 1 additional study and could not be separated.[49]

In our meta-analysis, the risk of reoperation was 47% lower in colorectal resections that used ICGFI compared with those that did not (RR 0.53, 95% CI 0.34 to 0.81; Figure 3), corresponding to an absolute effect of 18 fewer reoperations per 1,000 (from 25 fewer to 7 fewer). The estimate of effect was similar across the RCTs and nonrandomized studies (test for subgroup effect, *P* = .36; Figure 3).

We rated the certainty of the body of evidence for this outcome as Low (nonrandomized studies; RCTs downgraded for imprecision and indirectness; Appendix 2, Table A3).

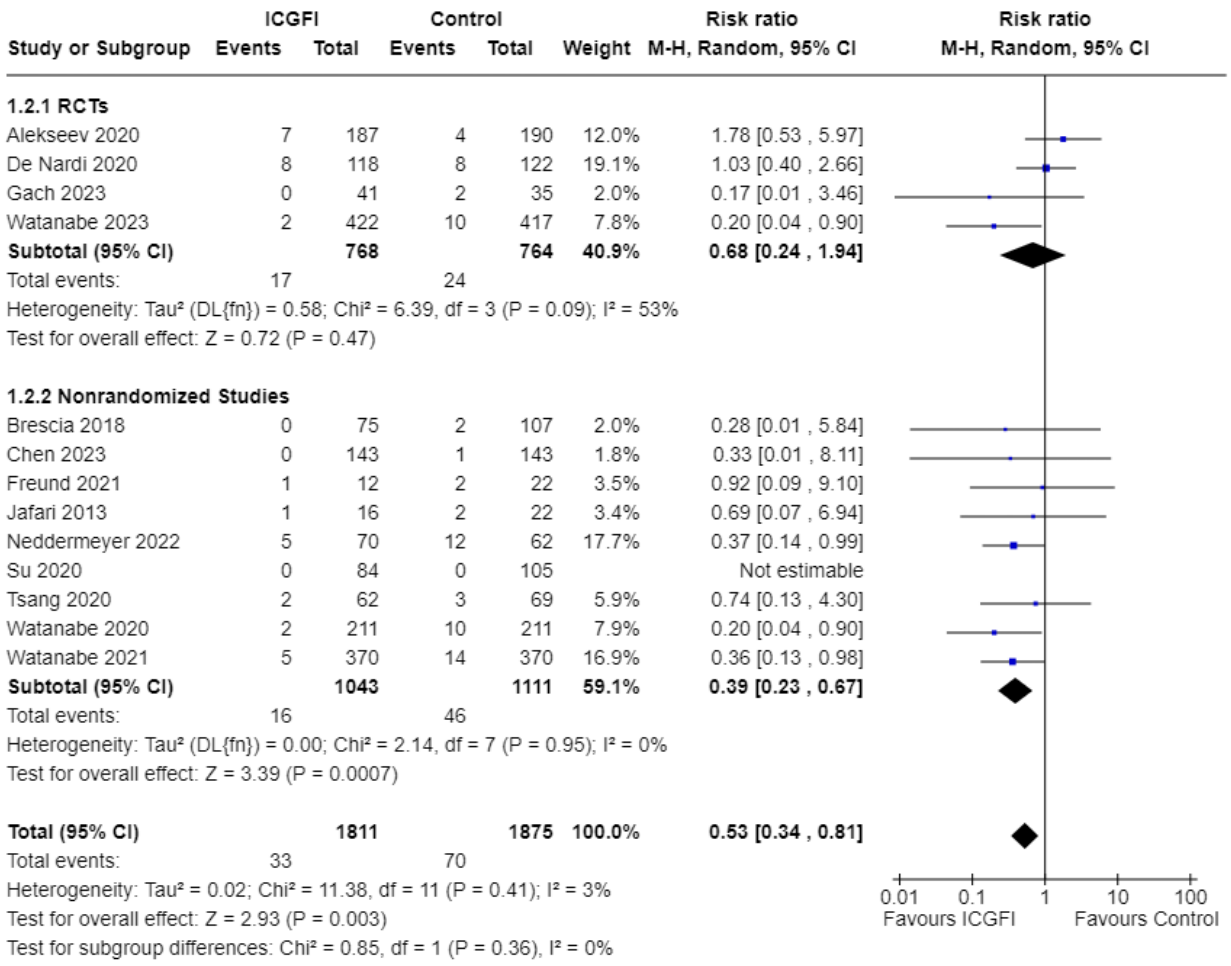

Figure 3: Reoperation Following Colorectal Resection, With ICGFI Versus Without

Abbreviations: CI, confidence interval; ICGFI, indocyanine green fluorescence imaging; M-H, Mantel-Haenzel; RCT, randomized controlled trial.

Sepsis

One RCT[34] and 2 nonrandomized comparative studies[31,46] reported sepsis between study participants who underwent surgery with ICGFI versus without. De Nardi et al[34] reported 1 case (0.4% of all study participants, n = 240) of septic shock due to AL in the control group, which was fatal. Jafari et al[31] reported that 6% of participants in the ICGFI group and 13% of participants in the control group experienced sepsis (*P* values not reported, and we were unable to back-calculate n per group to replicate the percentages reported).

In the study by Tueme-de la Peña et al,[46] cases were reported as either focal sepsis (ICGFI group, n = 5 [6%]; control group, n = 1 [1.2%]) or generalized sepsis (0 cases in the ICGFI group; 1 case in the control group [1.2%]); these differences were not statistically significant (*P* = .115 and .999, respectively).

We rated the certainty of the body of evidence for this outcome as Low (RCTs, downgraded for imprecision) to Very low (nonrandomized studies, downgraded for imprecision and risk of bias; Appendix 2, Table A3).

Length of Hospital Stay

Fifteen studies reported length of hospital stay (Table 8).[31,33-38,40,42,44-49] Across studies, length of stay (median or mean) appeared to be numerically similar in the ICGFI and control groups (i.e., ≤ 1 day difference). Among the studies that statistically compared length of stay between the ICGFI and control groups, 12 of 15 reported no statistically significant difference (Table 9).[33,34,36-38,40,42,44-46,48,49]

One RCT[35] and 1 nonrandomized study[47] analyzed the between-groups difference in number of days in hospital and found a statistically significantly longer length of stay in the control group ($P < .05$). In an analysis of mean difference between groups, Watanabe et al (2020)[47] reported a statistically significant mean reduction of 2.62 days in the ICGFI group compared with the control group (95% CI 0.96 to 4.28, $P = .002$).

We rated the certainty of the body of evidence for this outcome as Moderate (RCTs, downgraded for imprecision) to Low (nonrandomized studies; Appendix 2, Table A3).

Table 8: Length of Stay Following Colorectal Resection, With ICGFI Versus Without

Author/trial name, year	ICGFI, MD, d (range), or MN, d (SD)	Control, MD, d (range), or MN, d (SD)	*P* value
AVOID trial, 2024[49]	MD: 4 (IQR: 3–6)	MD: 4 (IQR: 3–5)	.34
De Nardi et al, 2020[34]	MD: 6 (5–52)	MD: 7 (4–24)	ns
EssentiAL trial, 2023[36]	MD: 13 (IQR: 9–16)	MD: 13 (IQR: 10–17)	.221
FLAG trial, 2020[33]	MD: 8 (4–32)	MD: 8 (4–32)	ns
Gach et al, 2023[35]	MN: 4.4 (0.8)	MN: 4.9 (2.5)	.047
Brescia et al, 2018[37]	MN: 4.4 (0.7)	MN: 4.6 (0.9)	ns
Chen et al, 2023[38]	MD: 10 (7–18)	MD: 10 (8–19)	.243
Freund et al, 2021[40]	MD: 4 (2–21)	MD: 4.5 (3–21)	.34
Jafari et al, 2013[31]	MD: 4 (NR)	MD: 5 (NR)	NR
Neddermeyer et al, 2022[42]	MD: 10 (7–44)	MD: 11 (5–94)	.1872
Su et al, 2020[44]	MN: 5.7 (1.4)	MN: 6.0 (1.5)	.139
Tsang et al, 2020[45]	MD: 7 (4–27)	MD: 7 (7–45)	.956
Tueme-de la Peña et al, 2023[46]	MD: 6 (IQR: 4–8)	MD: 6 (IQR: 4–8)	.577
Watanabe et al, 2020[47]	MD: 9 (4–77)	MD: 12 (4–73)	.002
Watanabe et al, 2021[48]	MD: 7 (IQR: 6–8)	MD: 7 (IQR: 6–9)	.256

Abbreviations: ICGFI, indocyanine green fluorescence imaging; IQR, interquartile range; MD, median; MN, mean; NR, not reported; ns, not statistically significant; SD, standard deviation.

Mortality

Thirteen studies reported postoperative mortality (Table 9).[32-37,39,40,42,44,47-49] Six reported no deaths in either the ICGFI or control group,[33,36,40,42,44,47] and 1 reported no mortality due to AL during the study.[35] Two RCTs reported a single death in the control group only.[32,34] No statistically significant differences in mortality were noted among the 4 studies that conducted statistical analyses.[37,39,48,49]

The other included studies did not report postoperative mortality.[31,38,41,43,45,46]

We rated the certainty of the body of evidence for this outcome as Very low (RCTs, downgraded for serious limitations in imprecision and risk of bias; nonrandomized studies, downgraded for limitations in imprecision; Appendix 2, Table A3).

Table 9: Mortality Following Colorectal Resection, With ICGFI Versus Without

Author/trial name, year	ICGFI, n/N (%)	Control, n/N (%)	Details, if provided	*P* value
AVOID trial, 2024[49]	10/463 (2)	8/468 (2)	Within 90 d of surgery[a]	.62
	9/463 (2)	6/468 (1)	Within 30 d of surgery[a]	.42
De Nardi et al, 2020[34]	0/118 (0)	1/122 (0.8)	Death related to septic shock following AL	–
EssentiAL, 2023[36]	0/422 (0)	0/417 (0)	–	–
FLAG, 2020[33]	0/187 (0)	0/190 (0)	Within 30 d of surgery	–
Gach et al, 2023[35]	0/41 (0)	0/35 (0)	Death due to AL	–
PILLAR III trial, 2021[32]	0/178 (0)	1/169 (0.6)	–	–
Brescia et al, 2018[37]	0/75 (0)	1/107 (0.9)	–	ns[b]
Flores-Rodrigues et al, 2023[39]	5/280 (1.8)	12/505 (2.4)	–	.57
Freund et al, 2021[40]	0/12 (0)	0/24 (0)	–	–
Neddermeyer et al, 2022[42]	0/70 (0)	0/62 (0)	–	–
Su et al, 2020[44]	0/84 (0)	0/105 (0)	–	–
Watanabe et al, 2020[47]	0/211 (0)	0/211 (0)	–	–
Watanabe et al, 2021[48]	0/370 (0)	1/370 (0.3)	Occurred before postoperative day 30	.317

Abbreviations: AL, anastomotic leak; ICGFI, indocyanine green fluorescence imaging; ns, not statistically significant.

[a]Causes of death not reported by intervention group.

[b]*P* value not reported.

Ongoing Studies

We are aware of the following ongoing studies that may have potential relevance to our research question, all registered on ClinicalTrials.gov (Table 10).

Table 10: Ongoing Studies

Title	Study type	Trial number	Details	Planned date to complete data collection
Perfusion Outcomes With Near Infrared-Indocyanine Green Imaging System in Laparoscopic Total Mesorectal Excision for Mid- or Low-rectal CanceR (POSTER)	RCT	NCT04012645	Comparing ICGFI vs. standard perfusion assessment in laparoscopic rectal excision	December 2023
The Prognosis of Colorectal Cancer Patients After Indocyanine Green Fluorescence-Guided Radical Surgery	Nonrandomized comparative	NCT06508541	Comparing ICGFI vs. standard perfusion assessment in complete or total mesocolic excision for colorectal cancer	September 2024
Intraoperative Indocyanine Green Fluorescence Angiography in Colorectal Surgery to Prevent Anastomotic Leakage (FLUOCOL-1)	RCT	NCT05168839	Comparing ICGFI vs. standard perfusion assessment in open, laparoscopic, or robotic-assisted left colectomy or high rectal resection	October 2025

Further, the included article by Gach et al[35] was a preliminary analysis of an RCT, for which further results may be published given that, at the time of writing, the study was listed as "recruiting" on ClinicalTrials.gov (NCT05263336).

Discussion

Similar to previously published evidence syntheses, the results of this systematic review show that the use of ICGFI reduces the occurrence of AL in colorectal surgery. Doing as much as possible to prevent AL in colorectal surgery is essential for patient safety and outcomes but is challenging given the multiple risk factors, including the patient's sex, age, nutritional status, radiation status, tumour location, and tissue viability and mechanical integrity,[31] among others. The proportion of ALs that can be attributed to compromised tissue perfusion at the anastomosis site is unknown.[55]

Our systematic review examined the evidence for numerous surgeries and indications for colorectal resection. Given that surgical approach influences neither bowel perfusion nor anastomotic healing,[42] we examined open, laparoscopic, robotic-assisted, and transanal colorectal surgeries.

Although AL is a relatively objective event, the definition of AL varied across the included studies; some included leaks requiring reoperation; some included pelvic abscesses (e.g., requiring percutaneous drainage), and some included subclinical leaks (on radiologic findings only). Broader definitions of AL will yield a higher number of events; however, some of the events will be of less clinical severity than others. Similarly, the severity classification used in the studies varied between the ISREC and Clavien-Dindo systems, both of which are clinically appropriate but add yet more variability to the literature. These are well-known challenges for evidence synthesis.

The included studies primarily comprised participants undergoing low anterior or rectal resections, in some cases alongside participants undergoing other types of colectomies. This may not be surprising as there tends to be greater concern about AL when the anastomosis is lower. For instance, some RCTs of low anterior resections have estimated an AL rate ranging from 2% to 12%.[56,57] We conducted subgroup analyses to explore potential effects within the various types of colorectal resections reported in the studies; however, the subgroups lacked statistical power, and the analyses did not suggest clear trends.

The body of included evidence comprises studies conducted in a number of international locations; however, we cannot comment on the study participants or which populations were or were not represented (e.g., PROGRESS-Plus characteristics) as no such information was reported.

The data reported for the outcomes of readmission, reoperation, and mortality in most studies provided little or no detail about the antecedents to these events. It is unknown whether the occurrences observed in the studies were attributable to AL or to another perioperative complication (e.g., infection). Other outcome data were also unclear, for instance when reports of sepsis were combined with reports of all other complications.[47]

We were unable to quantitatively synthesize some outcomes (e.g., length of hospital stay) because of methodological heterogeneity or variation in the data reported between studies. Our exploratory subgroup analyses of AL may suggest directions for further research.

Our evidence synthesis is up to date and includes the most recently published studies at the time of writing. We included both RCTs and nonrandomized studies to complement each other[58] and capture the best available evidence to inform policy decision-making.[59] To minimize the elevated risk of confounding, time bias, selection bias, and other biases that can be introduced in some types of nonrandomized studies, we included only comparative cohort studies with contemporaneous controls.

Conclusions

The evidence from RCTs and nonrandomized studies suggests that, compared with visual assessment alone, the addition of ICGFI to assess anastomotic perfusion during colorectal surgery:

- Reduces ALs (GRADE: Low) (pooled RR 0.58 [95% CI 0.47 to 0.72]; absolute effect: 32 fewer cases per 1,000, from 40 fewer to 21 fewer)
- May have little to no effect on hospital readmission (GRADE: Low)
- Reduces reoperation (GRADE: Low) (pooled RR 0.53 [95% CI 0.34 to 0.81]; absolute effect: 18 fewer cases per 1,000, from 25 fewer to 7 fewer)
- May reduce sepsis slightly; however, the evidence is very uncertain (GRADE: Very low to Low)
- Has little to no effect on length of hospital stay (GRADE: Low to Moderate)

Further, the effect of ICGFI on mortality is very uncertain (GRADE: Very low).

Economic Evidence

Research Question

What is the cost-effectiveness of indocyanine green fluorescence imaging (ICGFI) compared with visual assessment alone for the visualization of anastomotic perfusion during colorectal surgery?

Methods

Economic Literature Search

We performed an economic literature search on January 30, 2024, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them until September 3, 2024. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from inception to search date
- Cost–benefit analyses, cost-effectiveness analyses, or cost–utility analyses

Exclusion Criteria

- Narrative reviews, editorials, case reports, commentaries, and abstracts

Population

Inclusion Criteria

- Adults (aged 18 years and older) undergoing colorectal surgery requiring the creation of an anastomosis for malignant or benign conditions, including colorectal cancer, diverticulitis, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), and bowel obstruction)

Exclusion Criteria

- Individuals undergoing colorectal surgery that does not involve the creation of an anastomosis in the colon

Intervention

Inclusion Criteria

- Use of ICGFI to visualize anastomotic perfusion

Exclusion Criteria

- Use of other methods or technologies to visualize anastomotic perfusion
- Use of ICGFI for other purposes (e.g., sentinel node biopsy)

Comparators

Inclusion Criteria

- Visual assessment alone to assess anastomotic perfusion, specifically:
  - Assessing perfusion under white light based on the colour of the tissue (pink indicating well-perfused tissue)
  - Palpable pulse in mesentery
  - Pulsatile arterial bleeding (i.e., assessing perfusion based on whether pulsatile bleeding is seen at the divided edge of the bowel or the marginal vessel)
  - Use of technologies such as a Woods lamp, Doppler ultrasound, flowmetry, tonometry, or spectroscopy

Exclusion Criteria

- Any alternative methods or technologies used to assess anastomotic perfusion that are not based on visual assessment alone

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALYs])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[50] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom.[60] The NICE checklist has 2 sections: the first is for assessing study applicability, and the second is for assessing study limitations. We modified the wording of the questions of the first section to make it specific to Ontario. Using this checklist, we assessed the applicability of each study to the research question (directly, partially, or not applicable). Next, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be applicable.

Results

Economic Literature Search

The economic literature search yielded 28 citations, including grey literature results and after removing duplicates, published between database inception and January 30, 2024. We identified no additional eligible studies from other sources, including database alerts (monitored until September 3, 2024). In total, we identified 2 studies that met our inclusion criteria. See Appendix 4 for a list of selected studies excluded after full-text review. Figure 4 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

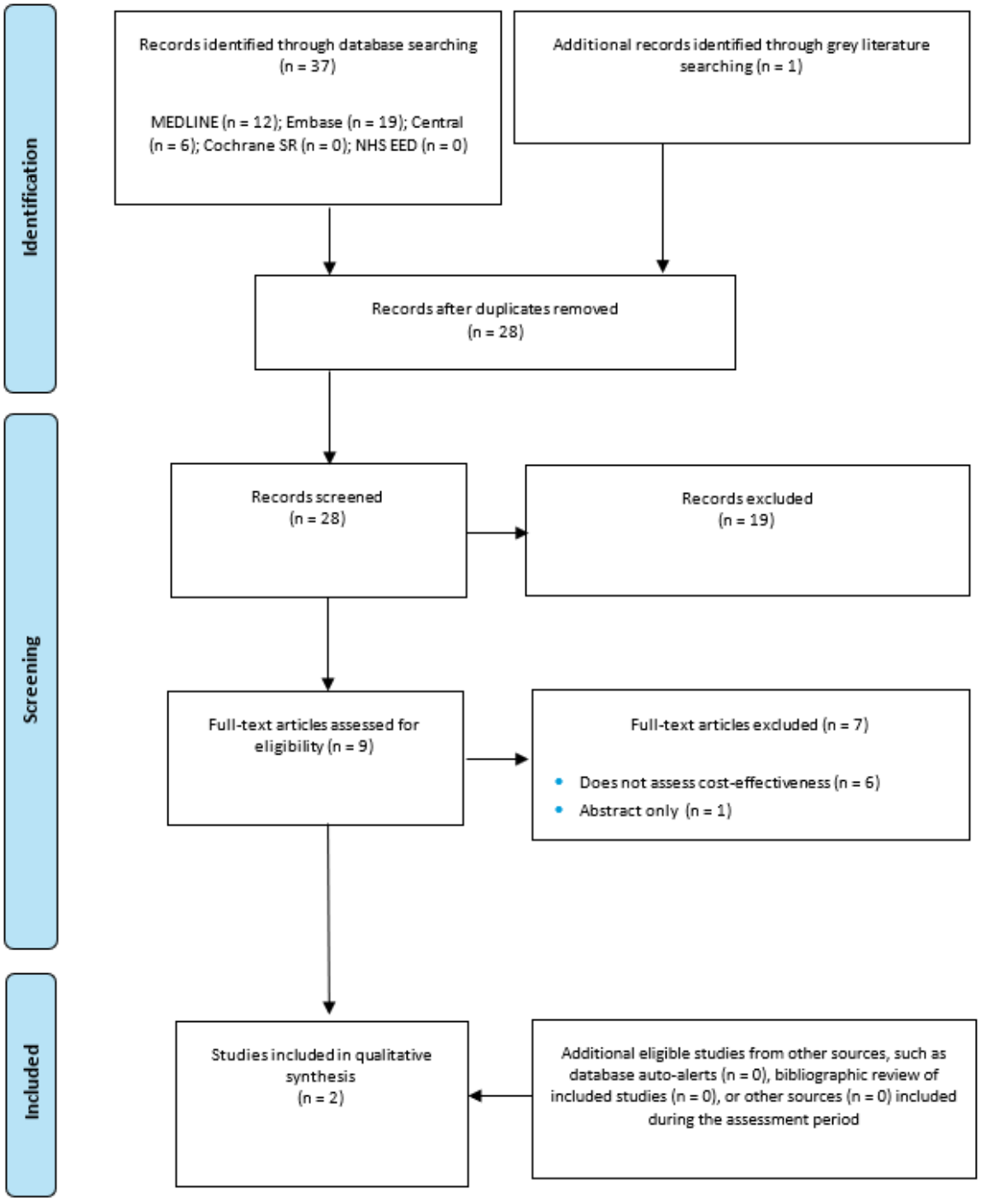

Figure 4: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic systematic review. The economic literature search yielded 28 citations, including grey literature results and after removing duplicates, published between database inception and January 30, 2024. We screened the abstracts of the 28 identified studies and excluded 19. We assessed the full text of 9 articles and excluded a further 7. In the end, we included 2 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[50]

Overview of Included Economic Studies

We conducted an economic evidence review to identify any relevant economic evaluations assessing the cost-effectiveness of ICGFI compared with visual assessment alone for the visualization of anastomotic perfusion during colorectal surgery. Our economic evidence review identified 2 Canadian economic studies,[19,61] of which 1 was directly applicable[19] and 1 was partially applicable[61] to our research question. Both studies were conducted using a Canadian perspective.

Liu et al[61] conducted a model-based cost–consequence analysis conducted from the hospital payer perspective, though the province of that perspective was not specified. However, cost parameters were obtained from a retrospective administrative analysis of all colon and rectal resection surgeries with anastomosis conducted in Canada (excluding Quebec) between 2008 and 2015.[62] The authors did not report the time horizon or discount rate used, but it can be inferred that the model duration was short term; thus, the results were not discounted.[61] Liu et al[61] found that compared with standard care (i.e., visual assessment alone), the use of ICGFI resulted in cost savings attributed to the reduction of anastomotic leaks (ALs), which are associated with an average per-leak cost of $9,934.50 to the public health system. The costs associated with ALs avoided completely offset the upfront direct cost of ICGFI use, which was estimated to be $250 per patient ($200 per dose of ICG dye + $50 per-surgery capital cost). While no probabilistic sensitivity analysis was conducted, a 1-way deterministic sensitivity analyses found that ICGFI was no longer cost-saving when the complication cost of an AL was less than $5,616.29 or when the per-patient cost of ICGFI was greater than $634.44.

The second study, conducted by the Centre for Clinical Epidemiology and Evaluation at the University of British Columbia, was conducted as part of a health technology assessment (HTA) for the BC Health Technology Review Office.[19] This HTA evaluated the safety, effectiveness, cost-effectiveness, and budget impact of publicly funding ICGFI for the visualization of anastomotic perfusion in colorectal surgeries performed in British Columbia. The authors conducted a model-based cost–utility analysis from the public payer perspective using a 20-year time horizon. Both cost and effectiveness outcomes were discounted by 3%. The authors found that ICGFI was dominant (i.e., more effective and less costly) compared with standard care. All upfront direct costs of ICGFI were redacted in the study. However, as in the study by Liu et al,[61] the authors attributed the cost savings associated with the ICGFI strategy to the reduction in ALs and the subsequent reduction in costs associated with managing this major complication.[19] A probabilistic sensitivity analysis showed that at a willingness-to-pay (WTP) of $50,000 per QALY, the probability of ICGFI being cost-effective was 88%.[63] Moreover, at a WTP of $0, the probability of ICGFI being cost-saving was 61%.[19] ICGFI remained the dominant strategy in most deterministic sensitivity analyses. However, ICGFI resulted in an incremental cost-effectiveness ratio (ICER) higher than the commonly accepted WTP of $50,000 per QALY in the following scenarios: (1) when the baseline rate of ALs was extremely low (i.e., 2%–4%, or 70% lower than in the reference case); (2) when ICGFI reduced the rate of ALs by less than 21% compared with standard care; and (3) when there was a substantial reduction in the gap in costs between patients who did and did not experience major complications. ICGFI was also found no longer to be cost-effective when the capital cost per surgery with ICGFI surpassed a particular cutoff point; however, information on this threshold was redacted.

Table 11 summarizes the characteristics of the 2 included studies.

Table 11: Characteristics of Studies Included in the Economic Literature Review

	Analysis						Results		
Author, year, country, intervention, comparator	**N**	**Technique**	**Design (model)**	**Approach or perspective**	**Time horizon (discount rate)**	**Study population**	**Health outcomes**	**Costs**	**Cost-effectiveness**
Liu et al, 2022, Canada[61]		Cost–consequence analysis	Decision tree	Hospital payer perspective	NR (NR)	Patients undergoing colorectal surgery	NA	Currency, year: CAD, 2020 Mean cost difference, I vs C: –$192.22	I vs C: cost-saving A PSA was not conducted. A 1-way DSA found that ICGFI was no longer cost-saving when the cost of treating an AL was < $5616.29 or when the per-patient cost of ICGFI was > $634.44.
I: ICGFI	—	—	—	—	—	—	—	Mean cost: : $9,315.07	—
C: White light	—	—	—	—	—	—	—	Mean cost: : $9,507.29	—
Centre for Clinical Epidemiology and Evaluation, 2017, Canada[19]		Cost–utility analysis	Decision tree and Markov Model	Public payer perspective	20 y (3%)	Patients undergoing colorectal surgery	Mean QALY difference, I vs C: 0.050	Currency, year: CAD, 2015 Mean cost difference, I vs C: –$905.00	I vs C: dominant A PSA showed that at a WTP of $50,000/QALY, the probability of ICGFI being cost-effective was 88%. ICGFI remained dominant in most DSAs but resulted in an ICER higher than $50,000/QALY in 3 scenarios: (1) when the baseline leak rate was 70% lower than in the reference case; (2) when the decrease in leak rate with ICGFI was less than 21% (OR = 0.785); and (3) when the cost incurred by a patient with a major complication was less than 30% more than the cost incurred by a patient without complications.[a]
I: ICGFI	—	—	—	—	—	—	Mean QALY: 8.559	Mean cost: $28,811	—
C: White light	—	—	—	—	—	—	Mean QALY: 8.510	Mean cost: $29,716	—

Abbreviations: AL, anastomotic leak; C, comparator; CAD, Canadian dollars; DSA, deterministic sensitivity analysis; I, intervention; ICGFI, indocyanine green fluorescence imaging; NA, not applicable; NR, not reported; OR, odds ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

[a]ICGFI was also found no longer to be cost-effective when the capital cost per surgery under this strategy surpassed a cutoff point; however, information on this threshold was redacted.

Applicability and Limitations of the Included Studies

Appendix 5 (Tables A4 and A5) provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. One was deemed directly applicable to our research question,[19] and 1 was deemed partially applicable.[61] We assessed the limitations of both studies as minor.

Discussion

Our economic evidence review found that ICGFI may be either cost-saving or dominant (i.e., more effective and less costly) compared with standard care (i.e., visual assessment alone).[19,61]

The study by Liu et al[61] was a cost–consequence analysis that reported only cost outcomes. No probabilistic sensitivity analysis was conducted, but a deterministic sensitivity analysis found that results were sensitive to the costs associated with ALs and the overall direct cost of ICGFI use. A limitation of this study is that it excluded all costs associated with physician remuneration. Further, the authors considered only the costs of simple percutaneous drainage and antibiotics in its estimate of costs associated with ALs. While minor ALs can be managed by these approaches, major ALs require reoperation and an increase in length of hospital stay.[1] As such, the authors underestimated the costs associated with ALs. However, given that ICGFI was found to be cost-saving even with these conservative cost estimates, it is unlikely that the authors' overall conclusion that ICGFI is cost-effective would change were additional complication costs to be considered.

The study conducted by the Centre for Clinical Epidemiology and Evaluation similarly found that ICGFI was cost-effective compared with standard care.[19] Reference case results remained robust in a probabilistic sensitivity analysis. A deterministic sensitivity analysis identified that the drivers of cost-effectiveness included the baseline risk of AL, the treatment effect of ICGFI on the risk of AL, and the cost associated with this major complication. Although this analysis was deemed to be directly applicable to our research question, we are uncertain about the cost-effectiveness of ICGFI in Ontario for 2 reasons. First, all cost parameters associated with ICGFI (i.e., the acquisition cost of a near-infrared imaging system and the costs of ICG dye and annual maintenance) were redacted in this report. As such, we were unable to determine whether the reported unit cost of ICGFI is similar to what it would be in Ontario today. Second, the per-surgery capital cost of the near-infrared imaging system required for ICGFI use was estimated based on the projected annual volume of colorectal surgeries in British Columbia and thus may not reflect the Ontario context.

Notably, across both studies,[19,61] the effectiveness of ICGFI was derived from systematic reviews[19,64] that are now outdated. Liu et al[61] derived this key parameter from a meta-analysis of 20 comparative studies[64] (including 2 randomized controlled trials [RCTs][33,34]) and found that the pooled estimate of the odds ratio for ALs was 0.46 (95% confidence interval [CI] 0.34, 0.62; P = .00001), favouring ICGFI. The study by the Centre for Clinical Epidemiology and Evaluation[19] derived this key parameter from 4 nonrandomized comparative studies and 1 single-arm study and found that the pooled estimate of the risk ratio for ALs was 0.55 (95% CI 0.35, 0.86; P = .009), favouring ICGFI. Since the publication of both studies, 4 new RCTs have become available.[32,35,36,49] Because the effect of ICGFI on the reduction of risk of anastomotic leakage is a key driver of cost-effectiveness results, these more recently published RCTs must be assessed to identify the best available evidence on this clinical parameter today.

Equity Considerations

Neither included study identified equity issues in its assessment process nor incorporated equity-related factors into its analyses.

Strengths and Limitations

Our economic evidence review is a comprehensive review of the literature as we retrieved studies published from database inception until our search date. Further, we performed a grey literature search and reviewed the reference lists of the included studies for any additional studies not identified by our search strategy. As such, it is unlikely that we missed any relevant studies. We also critically appraised the applicability of the studies to our research question and their limitations using a modified quality appraisal checklist for economic evaluations developed by NICE.[60]

Both included studies were conducted in Canada, and both found that ICGFI was either dominant[19] or cost-saving[61] compared with standard care. However, neither study considered Ontario's colorectal surgery volumes in their estimate of the costs associated with ICGFI. Since some cost parameters (e.g., the capital cost of purchasing a near-infrared imaging system) are volume dependent, it is important to incorporate such parameters from the context of Ontario to adequately determine the cost-effectiveness of ICGFI in the province.

Conclusions

We identified 2 economic analyses relevant to our research question.[19,61] Both were Canadian studies that found ICGFI to be either dominant[19] or cost-saving[61] compared with standard care. Further, the results of both remained largely robust across sensitivity analyses. However, neither study incorporated volume-dependent cost parameters from an Ontario-specific context. And since the publication of these studies, 4 new RCTs have become available.[32,35,36,49] As such, to ensure that our clinical parameters and estimates of resource use were obtained from the best available sources and would be generalizable to the Ontario setting, we conducted a primary economic evaluation. For this evaluation, we adapted the model used in the study by the Centre for Clinical Epidemiology and Evaluation[19] and incorporated more recent clinical evidence and Ontario-specific data from a clinical administrative database maintained by the Canadian Institute for Health Information.

Primary Economic Evaluation

While the published economic evaluations[19,61] identified in the economic literature review addressed our research question, neither included the most up-to-date clinical or cost evidence nor considered Ontario's colorectal surgery volumes. As such, we conducted a primary economic evaluation to ensure that our clinical parameters and estimates of resource use were obtained from the best available sources and would be generalizable to the Ontario setting. To leverage existing work, we adapted the model used in the study by the Centre for Clinical Epidemiology and Evaluation[19] and incorporated clinical evidence that has become available since the publication of the studies included in the economic literature review, as well as Ontario data from a clinical administrative database maintained by the Canadian Institute for Health Information.

Research Question

What is the cost-effectiveness of indocyanine green fluorescence imaging (ICGFI) compared with visual assessment alone for the visualization of anastomotic perfusion during colorectal surgery from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[65] The content of this report is based on a previously developed economic project plan.

Type of Analysis

We conducted a cost–utility analysis, as recommended by Canada's Drug Agency (CDA; formerly the Canadian Agency for Drugs and Technologies in Health [CADTH]) guidelines for economic evaluations.[66] For the effectiveness outcome measure, we used quality-adjusted life-years (QALYs), which consider both survival and health-related quality of life. A generic outcome measure such as the QALY allows decision-makers to make comparisons across different conditions and interventions.

We also conducted a cost-effectiveness analysis with the following effectiveness outcomes:

- Total number of major anastomotic leaks (ALs) per 1,000 patients
- Total number of major ALs avoided per 1,000 patients
- Number needed to treat (NNT) to prevent an additional major AL compared with standard care (i.e., visual assessment alone)

Population of Interest

Our population of interest was adults (aged 18 years and older) undergoing colorectal surgery requiring the creation of an anastomosis for malignant or benign conditions, including colorectal cancer, diverticulitis, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), and bowel obstruction.

Because only limited data were available, we were unable to conduct an equity-related subgroup analysis. In Ontario, more research may be required to describe how various populations might access colorectal surgery using ICGFI.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

We conducted evaluations for ICGFI compared with visual assessment alone to assess anastomotic perfusion during colorectal surgery. Table 12 summarizes the interventions evaluated in the economic model.

Table 12: Disease Interventions and Comparators Evaluated in the Primary Economic Model

Intervention	Comparator	Population	Outcome
ICGFI	Standard care: visual assessment alone	Adults undergoing colorectal surgery for malignant or benign conditions, including colorectal cancer, diverticulitis, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), and bowel obstruction)	Incremental QALYs Incremental cost ICER ($/QALY) Total number of major ALs per 1,000 patients Total number of major ALs avoided per 1,000 patients NNT to prevent an additional major AL compared with standard care

Abbreviations: AL, anastomotic leak; ICER, incremental cost-effectiveness ratio; ICGFI, indocyanine green fluorescence imaging; NNT, number needed to treat; QALY, quality-adjusted life-year.

Time Horizon and Discounting

The average age of our cohort is 65 years; thus, we used a 40-year time horizon in our reference case analysis to model a lifetime time horizon. This time horizon was appropriate to account for the differences in long-term costs, health outcomes, and complications between the intervention (ICGFI) and comparator (standard care [i.e., visual assessment alone]). In accordance with the CDA guidelines,[66] we applied an annual discount rate of 1.5% to both costs and effectiveness outcomes (including QALYs) incurred after the first year. All costs are expressed in 2024 Canadian dollars.

Main Assumptions

The model's main assumptions were as follows:

- For simplicity, we assumed that the treatment effect of ICGFI on the risk of developing an AL was similar across all indications and all sites where an anastomosis could be created.
  - We made this assumption because of the variability in the reporting of ALs in colorectal surgery with and without ICGFI by indication and by location of resection or anastomosis. Our clinical evidence review also included subgroup analyses to explore potential effects within the various

types of colorectal resections evaluated in the included studies. However, these analyses lacked statistical power and suggested no clear trends.

- Because the purpose of our model was to evaluate the impact of ICGFI on the cost and health outcomes associated with ALs, we did not further distinguish our population by surgical technique (e.g., laparoscopic vs. open) or by whether a stoma (an artificial permanent opening in the abdominal wall) was created during the index surgery. Our model was not intended to identify or incorporate any potential effects of surgical technique or stoma creation on clinical outcomes.
- We assumed that the mortality rate of patients with benign conditions, such as diverticulitis, Crohn's disease, ulcerative colitis, and bowel obstruction, was equal to that of the general population.
- We assumed that patients undergoing colorectal surgery for malignant conditions (i.e., colorectal cancer) would have a higher mortality rate in the first 5 years following the index surgery than those with benign conditions. After 5 years, the mortality of patients undergoing colorectal surgery for malignant conditions was assumed to be equal to that of the general population. This assumption considers that while the probability of death due to cancer in the next 5 years is higher in the colorectal cancer population than in the general population, the conditional survival rate in colorectal cancer patients increases over time, especially after surviving the first 5 years following diagnosis.[67]
- For simplicity, we modelled the excess mortality in colorectal cancer patients undergoing surgery in our model based on the 5-year net survival of colorectal cancer patients diagnosed with stage I, stage II, and stage III tumours. We took this approach because the first-line treatment for these tumours is typically colorectal surgery.[68] On the other hand, for stage IV tumours, surgery is only 1 of several treatment options, depending on various factors, including the site of metastases and the treatment intent (i.e., curative or noncurative).[68] As such, we expected that stage IV colorectal cancer tumours would make up a very small proportion of our model cohort. Therefore, when modelling excess cancer mortality in our model, we did not account for stage IV colorectal tumours.
- The definition of AL used in the included studies varied. For simplicity, we assumed that the postoperative mortality of patients with minor (ISREC grade B) ALs was equal to that of patients with no complications post-index surgery.
- In the ICGFI arm of the model, we assumed that each hospital had 1 near-infrared imaging system and that this was sufficient for all colorectal resection surgeries performed in the hospital.
- In the ICGFI arm of the model, we assumed that each hospital with a near-infrared imaging system would use ICGFI in 100% of their colorectal surgeries.
- We assumed the same acquisition cost for all near-infrared imaging systems using ICG, regardless of manufacturer.
- We assumed that ICGFI would not be used in any reoperations for ALs (D. Abramowitz, MD, email communication, June 20, 2024).
- Based on published AL management strategies, we assumed that all reoperations for AL would be laparotomies.[69]

Model Structure/Structure of the Analysis

To leverage existing work, we adapted the economic model from the study conducted by the Centre for Clinical Epidemiology and Evaluation[19] previously described in our economic evidence review. We made minor adjustments to the model structure, which were validated by local clinical experts. Further, we modified the clinical parameters to reflect the most updated evidence, and we modified the cost parameters to be specific to the Ontario setting.

The model is a decision-tree combined with a Markov model that simulates the relevant costs and health outcomes of adults undergoing colorectal surgery performed using ICGFI or standard care (i.e., visual assessment alone) to assess anastomotic perfusion (Figure 5). The decision-tree portion of the model represents the first 30 days post-index surgery, and the Markov portion of the model has a cycle of 1 year. The first Markov cycle captures the costs and effect outcomes of the decision-tree portion of the model. Depending on the treatment arm (ICGFI or standard care), patients will incur different costs and health outcomes.

Following the index surgery and primary anastomosis, all patients will enter the decision-tree portion of the model, where they may or may not experience an AL as a surgical complication. If patients do not experience an AL, they will remain alive until death. Patients who experience an AL may or may not require reoperation, depending on the severity of the leak. Those who do not require reoperation will accrue a utility decrement and some additional costs related to managing a minor AL but will remain alive until death.

On the other hand, patients with a major AL will require reoperation and often diversion (a redirection of part of the intestines to divert fecal matter away from the site and allow the new or reinforced anastomosis time to heal).[70] As such, patients who require reoperation for AL may or may not have a stoma created during the reoperation. Those who do not have a stoma created during this major procedure will remain alive until death. Those who have a stoma created may have the stoma reversed at a later time (typically within 12 months)[69,71] and will remain alive until death. Others will live with a permanent stoma until death.

In our model, a minor AL is defined as a grade B leak according to the International Study Group of Rectal Cancer (ISREC); such leaks require intervention but not reoperation.[51] A major AL is defined as ISREC grade C; such leaks require reoperation. Since ISREC grade A leaks do not require any change in patient management, for simplicity, we grouped patients with a grade A leak with those who did not experience an AL.

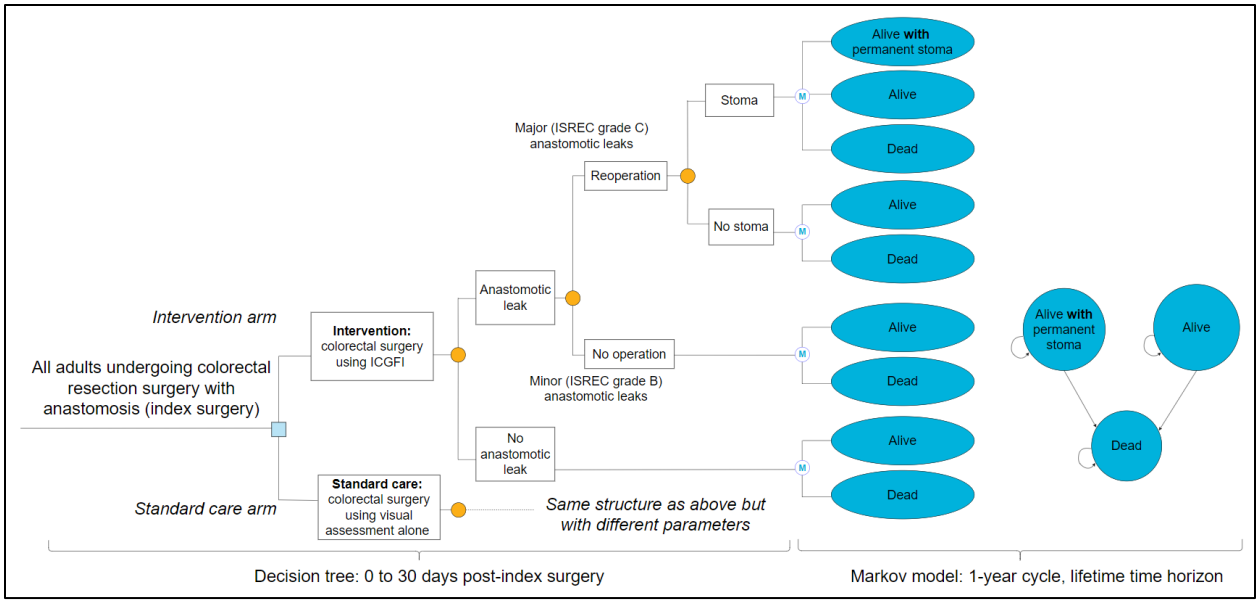

Figure 5: Model Structure

Abbreviations: ICGFI, indocyanine green fluorescence imaging; ISREC, International Study Group of Rectal Cancer.
Source: Modified based on Centre for Clinical Epidemiology and Evaluation, 2017.[19]

Clinical Outcomes and Utility Parameters

We used several input parameters to populate the model:

- Variables used to model the natural history of adults undergoing colorectal surgery for malignant or benign conditions
- Variables used to modify the natural history model to account for the treatment effect of ICGFI
- Variables used to capture health state utilities (i.e., quality of life)

Natural History

We based our population on the participants in the 19 studies included in the clinical evidence review. Because the crude estimate of the average age of all participants across these studies was 65 years, we used that age as the starting age of our model cohort.

We assumed that the proportion of our population with a malignant condition was similar to the proportion of patients with cancer undergoing colorectal surgery in British Columbia, which was reported to be 0.677 in the study by the Centre for Clinical Epidemiology and Evaluation.[19] We then estimated the distribution of our colorectal cancer population with stage I, II, and III tumours using data on incident colon cancer cases in Ontario by stage at diagnosis from a recent Cancer System Quality Index report.[72] This report found that in 2018, the distributions of incident colon cancer cases at stage I, stage II, stage III, stage IV, and unknown stage were 0.17, 0.27, 0.25, 0.22, and 0.09, respectively. The total distribution of incident colon cancer cases at stages I, II, and III was 0.69 (0.17 + 0.27 + 0.25). To

obtain the proportion of colorectal cancer patients undergoing surgery by stage for our cohort, we recalculated the distribution of cancer patients at stages I, II, and III out of the total distribution (0.69) of colon cancer patients diagnosed with stage I, II, and III tumours in Ontario.

For patients undergoing surgery for a benign condition, we estimated the baseline annual probability of death based on survival estimates for Ontario from Statistics Canada life tables for 2020 to 2022.[73]

For patients undergoing surgery for a malignant condition, we obtained the annual excess mortality in the first 5 years following the index surgery from the 5-year stage-specific net survival of people diagnosed with colorectal cancer in Canada (excluding Quebec) reported by Statistics Canada in 2023.[74] This report found that between 2010 and 2017, the 5-year net survival of people diagnosed with stages I, II, and III colorectal cancer was 0.95 (95% confidence interval [CI] 0.93 to 0.96), 0.87 (95% CI 0.86 to 0.88), and 0.71 (95% CI 0.69 to 0.72), respectively. For simplicity, we focused on the age group of 65 to 74 years. Based on these data, we calculated annual excess mortality by assuming a constant annual mortality rate. After the first 5 years following the index surgery, we assumed that the mortality rate of colorectal cancer patients was equal to that of the general population.

The baseline risk of developing an AL for patients undergoing colorectal surgery without ICGFI depends on many factors, including location of resection and location of anastomosis.[2,75] In general, the more distal an anastomosis is situated, the greater the risk of AL.[1] However, the incidence of ALs reported in the published literature ranges widely from 1.6% to 14.3% for ileocolic anastomoses, from 0.5% to 18% for colorectal anastomoses, and from 5% to 19% for coloanal anastomoses.[1] For simplicity, we used the median of the incidence of ALs (~9.75%) across ileocolic, colorectal, and coloanal anastomoses for the baseline risk of AL in our reference case.

We derived the likelihood of an AL being major (i.e., ISREC grade C) and thus requiring reoperation from a retrospective cohort study using colectomy data for 2012 to 2013 from the American College of Surgeons National Safety and Quality Improvement Program (ACS-NSQIP).[75] This study found that 54.8% of ALs following open resection or laparoscopic surgery of the colon were major leaks that required reoperation.

We obtained the likelihood of postoperative mortality following colorectal surgery from Bakker et al,[76] a retrospective study using data from the Dutch Surgical Colorectal Audit (DSCA) on patients undergoing surgery for colorectal cancer. This study found that the proportion of patients with major ALs who died within 30 days of surgery was statistically significantly higher than the proportion of patients without an AL who died within 30 days of surgery (16.4% vs. 3.1%, $P < .001$).[76] For our analysis, we made the simplifying assumption that the postoperative mortality rate of patients with a minor AL was equal to that of patients without an AL. Because postoperative mortality risk manifests within a short time following surgery, we modelled this risk only in the first cycle (i.e., the first year) of our Markov model.

Patients with a major AL require reoperation and often diversion.[70] We obtained the probability of stoma creation during reoperation from a population-based cohort study by Warps et al[77] that used DSCA data from patients who underwent colorectal surgery between 2013 and 2019. This study found that 79.5% patients who underwent reoperation for AL had a stoma created during the reoperation. Of these patients, 65.1% did not have their stoma reversed.[77]

Table 13 summarizes the natural history inputs used in the economic model.

Table 13: Natural History Inputs Used in the Economic Model

Model parameter	Mean (95% CI)	Distribution (parameter 1, parameter 2)	Reference
Proportion of patients undergoing colorectal surgery with anastomosis for a malignant condition	0.677 (NA)	Beta (14.13, 6,74)[a]	Centre for Clinical Epidemiology and Evaluation, 2017[19]
Proportion of patients with colorectal cancer undergoing colorectal surgery with anastomosis, by stage			
Stage I	0.25 (NA)	Fixed	CSQI, 2021[72,b]
Stage II	0.39 (NA)	Fixed	CSQI, 2021[72,b]
Stage III	0.36 (NA)	Fixed	CSQI, 2021[72,b]
Excess annual mortality among patients with colorectal cancer in the first 5 years following the index surgery compared with the general population, by stage			
Stage I	0.010 (0.008, 0.14)[c]	Beta (40, 3,897)[d]	Statistics Canada, 2023[74,e]
Stage II	0.027 (0.025, 0.029)[c]	Beta (562, 19,965)[d]	Statistics Canada, 2023[74,e]
Stage III	0.066 (0.064, 0.072)[c]	Beta (998, 14,081)[d]	Statistics Canada, 2023[74,e]
Basline risk of AL	0.0975 (NA)	Fixed	Ellis et al, 2021[1]
Probability of AL being major[f]	0.548 (0.513, 0.582)[c]	Beta (440, 363)[g]	Murray et al, 2016[75]
Postoperative mortality associated with a major AL	0.164 (0.144, 0.186)[c]	Beta (193, 983)[g]	Bakker at al, 2014[76]
Postoperative mortality asociated with a minor or no AL	0.031 (0.029, 0.034)[c]	Beta (455, 14,036)[g]	Bakker at al, 2014[76]
Probability of stoma creation during reoperation for AL	0.795 (0.766, 0.806)[c]	Beta (1,252, 340)[g]	Warps et al, 2022[77]
Probability of stoma being permanent[h]	0.651 (0.624, 0.677)[c]	Beta (815, 437)[g]	Warps et al, 2022[77]

Abbreviations: AL, anastomotic leak; CI, confidence interval; CSQI, Cancer System Quality Index; NA, not applicable.

[a]We estimated a beta distribution in a probabilistic analysis for this parameter with mean and an assumed standard error of 10% of the mean.

[b]We calculated this parameter from 2021 CSQIreport data on incident colon cancer cases in Ontario by stage at diagnosis. This report found that in 2018, the distributions of incident colon cancer cases at stage I, stage II, stage III, stage IV, and unknown stagewas 0.17, 0.27, 0.25, 0.22, and 0.09, respectively. The total distribution of incident colon cancer cases at stages I,II, andIII was 0.69 (0.17 + 0.27 + 0.25). To obtain the proportion of colon cancer patients undergoing surgery by stage for our cohort, we recalculated the distribution of cancer patients at stages I, II, and III out of the total distribution (0.69) of colorectal patients diagnosed with stage I, II, and III tumours in Ontario.

[c]We estimated the 95% CI for this parameter using mean, event number, and sample number.

[d]We estimated a beta distribution in a probabilistic analysis for this parameter with mean and variance.

[e]We calculated annual excess mortality from 5-year stage-specific net-survival data for Canada (excluding Quebec) from 2010 to 2017 as reported by Statistics Canada.[74] We assumed a constant annual mortality rate. For simplicity, we focused on excess mortality in the age group of 65 to 74 years.

[f] This parameter was calculated using data in Table 2 of Murray et al.[75] We considered minor leaks to be leaks treated with no intervention or percutaneous intervention, and major leaks to be leaks that required reoperation as treatment.

[f]We estimated a beta distribution in a probabilistic analysis for this parameter using number of events and sample size.

[g]We calculated this parameter using data reported by Murray et al (Table 2).[75] We considered minor leaks to be those treated with no intervention or percutaneous intervention and major leaks to be those requiring reoperation.

[h]In general, end stomas are permanent stomas, and defunctioning stomas are temporary stomas that are reversed once the underlying issue (e.g., risk of complications) is resolved. For this reason, we considered that the 819 patients who received an end stoma received a permanent stoma and that the 437 patients who received a defunctioning stoma received a temporary stoma. We calculated this parameter value (65.1%) based on the number of patients who received an end stoma (n = 819) out of the total number of patients who received a stoma during reoperation for an anastomotic leak (819 + 437 = 1,256).[77]

Impact of ICGFI on Natural History

We obtained the treatment effect of ICGFI on clinical outcomes from our clinical evidence review. We estimated the treatment effect as the risk ratio of having an AL following colorectal surgery using ICGFI

compared with standard care. We used the pooled estimate from the meta-analysis conducted in our clinical evidence review, which found that the pooled risk of AL was 42% lower with ICGFI than without (risk ratio 0.58, 95% CI 0.47 to 0.72). This pooled estimate was based on data reported in 19 studies (6 randomized controlled trials and 13 nonrandomized studies).

Table 14 provides the summary estimates used in the economic model.

Table 14: Summary Estimates (Relative Risks) Used in the Economic Model

Intervention	Variable	Relative risk (95% CI)	Distribution (parameter 1, parameter 2)	Reference
ICGFI	Treatment effect on risk of AL	0.58 (0.47, 0.72)	Lognormal (−0.54, 0.11)[a]	Clinical evidence review

Abbreviations: AL, anastomotic leak; CI, confidence interval; ICGFI, indocyanine green fluorescence imaging.

[a]We estimated a lognormal distribution in a probabilistic analysis for this parameter using mean of logs and standard deviation of logs.

Health State Utilities

A health state utility represents a person's preference for a certain health state or outcome, such as experiencing an AL following colorectal surgery. Utilities are often measured on a scale ranging from 0 (death) to 1 (full health).

For our analysis, we obtained the baseline utility of having survived the index colorectal surgery from a cost-effectiveness study by Jordan et al[78] that evaluated laparoscopic versus open colorectal resection using data collected via the EQ-5D-3L (a health-related quality-of-life instrument) in the 4 weeks following surgery.[78] Most colorectal surgeries in Ontario are performed laparoscopically.[79] As such, we used the baseline utility (0.83) of patients in the laparoscopic group for our reference case. Of note, this value was not statistically significantly different from that for the open-resection group (0.82).[78]

We obtained the utility decrement associated with living with a stoma from Dossa et al,[80] a systematic review and meta-analysis of health state utilities for patients with and without ileostomies and colostomies. This study found that the pooled mean utility obtained across studies (via the EQ-5D) for living with and without colostomy (a surgically created opening in the colon) was 0.79 (standard deviation [SD] 0.06) and 0.87 (SD 0.022), respectively. This study also found that utility values for living with an undifferentiated stoma (i.e., not specific to colostomy or ileostomy [a surgically created opening in the lowest part of the small intestine]) were similar to those reported for the colostomy and ileostomy health states. In our model, living with a stoma was therefore associated with a utility decrement of 0.08 (0.87 – 0.79 = 0.08) each year. For patients who had a stoma created during reoperation for an AL that was later reversed, this utility decrement was applied only to the first cycle of our Markov model. This estimate is similar to that reported in a systematic review of utility values of various health states for colorectal cancer patients.[81]

We found no studies that reported utilities for having an AL. We therefore used the proxy utility parameters reported in the study by the Centre for Clinical Epidemiology and Evaluation[19] for these events. For major ALs, we used the utility value (0.50) associated with having pain and surgical complications in patients with rectal cancer reported by Miller et al.[82] This study elicited utility values for various health states for patients with recurrent rectal cancer using the standard gamble technique from patient and health care provider perspectives.[82] For minor ALs, we used the utility decrement (0.02) associated with minor complications reported by Brasel et al.[83] This study, a cost–utility analysis evaluating management strategies for penetrating colon injuries, assigned an arbitrary utility decrement

of 0.02 to all minor complications associated with colorectal surgery. We applied the utility values associated with minor and major ALs only to the first cycle of our Markov model.

Table 15 lists the utilities used in the economic model.

Table 15: Utilities Used in the Economic Model

Health state or event	Mean (95% CI)	Duration	Distribution (parameter 1, parameter 2)	Reference
Baseline utility following index surgery	0.83 (0.79, 0.87)	1 y	Beta (3.22, 0.66)[a]	Jordan et al, 2014[78]
Utility after experiencing a major AL requiring reoperation	0.50 (0.38, 0.62)	1 y	Beta (0.99, 0.99)[a]	Miller et al, 2020[82]
Utility decrement asociated with a minor AL not requiring reoperation	0.02 (NA)	1 y	Gamma (100, 0.0002)[b]	Brasel et al, 1999[83]
Utility decrement associated with living with a stoma	0.08 (NA)[c]	1 y	Gamma (1.57, 0.05)[c]	Dossa et al, 2018[80]

Abbreviations: AL, anastomotic leak; CI, confidence interval; NA, not applicable.

[a]We estimated a beta distribution in a probabilistic analysis for this variable, and we calculated the shape parameters (alpha and beta) of this distribution using mean and variance.

[b]We estimated a gamma distribution in a probabilistic analysis for this variable, and we calculated the shape and scale parameters (alpha and theta) of this distribution using mean and an assumed standard error of 10% of the mean.

[c]We calculated the mean utility decrement associated with living with a stoma using the difference method.[84,85] Specifically, we calculated the mean and variance of the difference between the following 2 utility parameters from Dossa et al[80]: (1) the utility of patients living with colostomy: 0.79 (SD 0.06), and (2) the utility of patients living without colostomy: 0.87 (SD 0.022). We then estimated a gamma distribution in a probabilistic analysis for this variable, using the previously calculated mean and variance, to ensure a positive utility difference.[85]

Cost Parameters

We obtained our cost parameters from health administrative databases, the Ontario Health Insurance Plan (OHIP) Schedule of Benefits for Physician Services,[86] the Canadian Institute for Health Information (CIHI) Patient Cost Estimator tool,[87] the policies of the Ontario Ministry of Health's Assistive Devices Program,[88] and consultations with an ICGFI system manufacturer and clinical experts. All costs are reported in 2024 Canadian dollars.

Costs Associated With ICGFI

The main components of ICGFI are the acquisition cost of a near-infrared imaging system, which includes the first year of maintenance fees ($250,000), the ICG dye ($215), and the annual warranty and fees associated with maintaining the system after the first year ($18,500). These costs were provided by the manufacturer (Stryker Canada, email communication, May 22, 2024).

We calculated the per-surgery capital cost of ICGFI using the average of the individual hospital capital cost (IHCC) per surgery performed with ICGFI in Ontario:

$$IHCC = \frac{cost\ of\ acquiring\ ICGFI\ imaging\ system\ +\ maintenance\ cost\ over\ 10\ years}{\%\ of\ colorectal\ surgeries\ a\ hospital\ performs\ in\ ON\ \times projected\ number\ of\ colorectal\ surgeries\ for\ ON\ over\ 10\ years}$$

Because colorectal surgery is an inpatient procedure, we obtained the provincial average annual volume of colorectal surgeries with anastomosis from CIHI's Discharge Abstract Database (DAD)[89] via the IntelliHealth Ontario repository.[90] We used the relevant Canadian Classification of Health Intervention

(CCI)[91] codes to generate a dataset that captured all procedures involving colorectal surgery in Ontario from 2021 to 2023. Based on our dataset, we estimated that on average, 7,560 colorectal surgeries with anastomosis are performed in Ontario each year. (See Appendix 6, Tables A6 and A7, for further details.)

To calculate the IHCC per surgery, we limited our analysis to the hospitals that we are aware of that currently use ICGFI to assess anastomotic perfusion during colorectal resection surgeries, as these are considered high-volume hospitals for such procedures.

Using our DAD[89] dataset, we obtained the average annual number of colorectal surgeries with anastomosis performed at each of these hospitals. Based on these estimates, we approximated an average volume of 215 colorectal surgeries with anastomosis performed per year at each high-volume hospital.

We calculated the percentage of colorectal surgeries with anastomosis performed at each high-volume hospital as 2.8% (215 ÷ 7,560). Using the IHCC formula, we estimated that the capital cost per surgery using ICGFI is $194.

We did not consider costs associated with additional time for surgeons and operating room nursing staff to use ICGFI during colorectal surgeries in our analysis because there is currently no physician services billing fee associated with ICGFI use in Ontario. Further, the additional time that ICGFI adds to routine colorectal surgery is not substantial (D. Abramowitz, MD, telephone communication, November 11, 2023; U. Hameed, MD, telephone communication, October 16, 2023).

Costs Associated With Anastomotic Leaks

We obtained the hospital and procedure costs associated with ALs from the DAD,[89] the CIHI Patient Cost Estimator tool,[87] and the OHIP Schedule of Benefits for Physician Services[86] using the relevant CCI,[91] International Statistical Classification of Diseases and Related Health Problems (ICD),[92] and physician fee billing codes.

The treatment for a major (ISREC grade C) AL is reoperation, which often also requires diversion through the creation of a stoma.[70] The total procedure costs for a major AL with and without the creation of a stoma are $1,698.00 and $1,297.95, respectively. If a temporary stoma is created, the cost of the subsequent surgical procedure to reverse the stoma is $912.19. (See Appendix 6, Table A10, for further details.) For permanent stomas, we accounted for the annual cost of ostomy supplies at $975 per ostomy per year, based on the amount currently covered under Ontario's Assistive Devices Program.[88] In our model, we did not account for the cost of ostomy supplies associated with temporary stomas as patients accrue these costs out-of-pocket until the stoma is reversed.

We obtained the cost of hospitalization associated with reoperation for a major AL from a second dataset generated from the DAD[89] via IntelliHealth Ontario.[90] For this dataset, we used the relevant ICD code (T8183) to capture surgical procedures performed for postoperative ALs from 2021 to 2023. We subsequently filtered all cases with CCI codes starting with 1NM87, 1NM89, 1NM91, 1NQ87, and 1NQ89 to limit the dataset to surgical resections of the large intestine and rectum. Using this dataset, we estimated that the average total hospitalization cost associated with reoperation for a major AL is $62,000 per patient. (See Appendix 6, Table A8, for further details.)

We estimated the overall cost of physician services accrued during this hospital stay based on data obtained from the CIHI Patient Cost Estimator tool.[87] We calculated the ratio (0.22) of average hospital

cost to average physician cost during a hospital stay for the case mix group for colostomy and enterostomy in Ontario in 2021 and 2022. We then approximated the overall cost of physician services associated with a hospital stay following reoperation for a major AL at $13,140 per patient. Together, these estimates are similar to the range of hospitalization and physician services costs ($85,564 to $110,369) reported in the study by the Centre for Clinical Epidemiology and Evaluation[19] for reoperation for a major AL. The variation in this cost parameter between our estimate and that of the Centre for Clinical Epidemiology and Evaluation[19] may be explained by provincial differences. (See Appendix 6, Table A9, for further details.)

The most common nonoperative interventions for a minor (ISREC grade B) AL are antibiotics and percutaneous drainage of fluid. We estimated the average cost of antibiotics for patients with a minor AL to be $111 per leak, based on a typical antibiotic regimen. Specifically, we estimated this cost based on an average of 8.5 days of ceftriaxone at 1 g once a day plus metronidazole at 500 mg twice a day (D. Abramowitz, MD, written communication, March 6, 2024). Percutaneous drainage takes place in the operating room and is billed at $331.90. (See Appendix 6, Table A10, for further details.)

Table 16 summarizes the costs used in the economic model.

Table 16: Costs Used in the Economic Model

Variable	Mean (95% CI)	Distribution (parameter 1, parameter 2)	Duration or quantity	Reference
ICGFI components				
Capital cost per surgery using ICGFI	$194.00 (NA)	–	Per surgery	Calculated[a]
Near-infrared imaging system[b]	$250,000.00 (NA)	Fixed	–	Stryker Canada, email communication, May 22, 2024
Annual maintenance (after first year)	$18,500.00 (NA)	Fixed	–	Stryker Canada, email communication, May 22, 2024
Proportion of colorectal surgeries with anastomosis performed at a high-volume hospital in Ontario	0.028 (0.023, 0.034)[c]	Beta (97, 3,318)[d]	–	IntelliHealth Ontario (DAD), 2023[90]
Projected volume of colorectal surgeries with anastomosis performed in Ontario	7,560 (6,078, 9,042)[c]	Gamma (100, 75.60)[e]	Per year	IntelliHealth Ontario (DAD), 2023[90]
ICG dye	$215.00 (NA)	Fixed	Per surgery	Stryker Canada, email communication, May 22, 2024
Reoperation for a major (ISREC grade C) anastomotic leak – no stoma created				
Procedure (S167)	$1,297.95 (NA)	Fixed	Per surgery	OHIP Schedule of Benefits, 2024[86]
Reoperation for a major (ISREC grade C) anastomotic leak – stoma created				
Procedure (S167 + S157)	$1,698.00 (NA)	Fixed	Per surgery	OHIP Schedule of Benefits, 2024[86]
Ostomy supplies for permanent stoma	$975.00 (NA)	Fixed	Per year	Ontario Ministry of Health, 2024[88]
Surgical procedure to reverse a temporary stoma				
Procedure (S185)	$912.19 (NA)	Fixed	Per surgery	OHIP Schedule of Benefits, 2024[86]
Hospital stay associated with reoperation for a major (ISREC grade C) anastomotic leak				
Hospitalization	$62,000.00 ($49,848, $74,152)[c]	Gamma (100, 620)[e]	Per surgery	IntelliHealth Ontario (DAD), 2023[90]
Physician services during hospital stay	$13,141.00 (NA)	–	Per surgery	Calculated[f]
Ratio of physician service cost to hospitalization cost	0.22 (0.02, 0.41)[c]	Beta (3.42, 12.47)[d]	–	Calculated from CIHI Patient Cost Estimator, 2022[87]
Treatment for a minor (ISREC grade B) anastomotic leak				
Procedure (Z594)	$331.90 (NA)	Fixed	Per surgery	OHIP Schedule of Benefits, 2024[86]
Medications[e]	$111.00 ($89, $133)[g]	Gamma (100, 1)[e]	Per patient	ODB Formularly[93]

Abbreviations: CI, confidence interval; CIHI, Canadian Institute for Health Information; DAD, Discharge Abstract Database; ICG, indocyanine green; ICGFI, indocyanine green fluorescence imaging; ISREC, International Study Group of Rectal Cancer; NA, not applicable; ODB, Ontario Drug Benefit; OHIP, Ontario Health Insurance Plan.

[a]Calculated using the IHCC formula IHCC (see p. 60): ($250,000 + [18,500 × 9])/(2.8% x [7,560 × 10]) = $194 per surgery.

[b]The cost of acquiring a near-infrared imaging system incudes the first year of maintenance fees.

[c]We estimated the 95% CI around this parameter using the mean and an assumed standard error of 10% of the mean.

[d]We estimated a beta distribution in a probabilistic analysis for this variable, and we calculated the shape parameters (alpha and beta) for this distribution using mean and variance.

Notes for Table 16 continued

[e]We estimated a gamma distribution in a probabilistic analysis for this variable, and we calculated the shape and scale parameters (alpha and theta) for this distribution using mean and variance.

[f]Calculated by multiplying the hospitalization cost by the ratio of physician services cost to hospitalization cost: $62,000 × 0.22 = $13,141.

[g]Based on an average of 8.5 days of ceftriaxone at 1 g once a day plus metronidazole at 500 mg twice a day (D. Abramowitz, MD, written communication, March 6, 2024).

Internal Validation

The secondary health economist conducted formal internal validation. This process included testing the mathematical logic of the model, checking for errors, and ensuring the accuracy of parameter inputs and equations.

Equity Considerations

Several hospitals in Ontario have acquired near-infrared imaging systems to perform colorectal surgeries using ICGFI. Because ICGFI has been shown to reduce the risk of ALs in colorectal resection surgeries with anastomoses, it is important to ensure that high-volume hospitals for colorectal surgeries across Ontario have equitable access to this technology.

Analysis

Our reference case and sensitivity analyses adhered to Canada's Drug Agency (CDA) guidelines[66] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions.

We calculated the reference case of this analysis by running 5,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters expected to vary. We set distributions for variables within the model. Tables 13 to 16 list the model variables and corresponding distributions. We calculated mean costs with credible intervals, mean QALYs with credible intervals, and mean total number of major ALs per 1,000 patients with credible intervals for each intervention assessed. We also calculated mean incremental costs with credible intervals, mean incremental QALYs with credible intervals, mean total number of major ALs avoided per 1,000 patients with credible intervals, mean NNT to prevent an additional major AL with credible intervals, and the ICER for ICGFI versus standard care.

We present the results of the probabilistic analysis in a scatter plot on a cost-effectiveness plane and in a cost-effectiveness acceptability curve. Although $50,000 per QALY and $100,000 per QALY are not used as definitive willingness-to-pay (WTP) thresholds, graphical representations of the results relative to these guideposts facilitates interpretation of the findings and comparison with historical decisions.

We also present uncertainty quantitatively as the probability that an intervention is cost-effective at the commonly used WTP guideposts of $50,000 and $100,000 per QALY. Further, we present this uncertainty qualitatively in 1 of 5 categories defined by the Ontario Decision Framework[63]: highly likely to be cost-effective (80%–100% probability of being cost-effective), moderately likely to be cost-effective (60%–79% probability), uncertain if cost-effective (40%–59% probability), moderately likely not to be cost-effective (20%–39% probability), or highly likely not to be cost-effective (0%–19% probability).

Scenario Analyses

We conducted the following scenario analyses by modifying various parameter inputs and applying alternative assumptions:

- Scenario 1: Assumed a lower capital cost per surgery using ICGFI (50% of that in the reference case). This scenario considers that ICGFI may be used for indications other than colorectal surgery (e.g., other types of gastrointestinal surgeries, breast reconstructions, neurosurgeries), which would lower the capital cost per surgery using ICGFI.
- Scenario 2: Assumed a higher capital cost per surgery using ICGFI. This scenario considers that the hospitals currently using ICGFI to assess anastomotic perfusion during colorectal surgery are using the technology selectively because of the cost (D. Abramowitz, MD, telephone communication, December 4, 2023; U. Hameed, MD, written communication, May 12, 2024). We therefore assumed that these hospitals use ICGFI in 50% of the colorectal surgeries they perform.
- Scenario 3: Assumed a higher (125%) annual maintenance cost for an ICGFI system. The annual maintenance cost used in our reference case ($18,500) is the starting price of maintenance contracts for ICGFI components (Stryker Canada, email communication, May 22, 2024).
- Scenario 4: Assumed each vial of ICG dye is portioned for 3 uses (rather than 1 use, as in the reference case). This scenario reflects the current practice of some hospitals of using one-third of a vial per surgery.
- Scenario 5: Assumed a lower (85%) cost of both the near-infrared imaging system and the ICG dye. This assumption considers that the list price of ICGFI components may be discounted following price negotiations between a hospital and the manufacturer (Stryker Canada, email communication, May 22, 2024).
- Scenario 6: Applied a 3% discount rate to both costs and effectiveness outcomes. This scenario allowed us to compare our results with those of the report by the Centre for Clinical Epidemiology and Evaluation, which used this rate.[19]
- Scenario 7: Applied a 0% discount rate to both costs and effectiveness outcomes. This scenario was conducted as recommended in the CDA guidelines.[66]
- Scenario 8: Applied the baseline risk of AL for anastomoses created at the end of the ileum (at the end of the small intestine) and the beginning of the colon. For this scenario, we used the median (7.95%) of the range of incidence of ALs (1.6%–14.3%) reported in the literature for ileocolic anastomoses.[1]
- Scenario 9: Applied the baseline risk of AL for anastomoses involving the colon or the colon and rectum. For this scenario, we used the median (9.25%) of the range of incidence of ALs (0.5%–18%) reported in literature for colorectal anastomoses.[1]
- Scenario 10: Applied the baseline risk of AL for anastomoses involving the colon and anus. For this scenario, we used the median (12%) of the range of incidence of ALs (5%–19%) reported in literature for coloanal anastomoses.[1]

Table 17 summarizes the variables that we varied in the scenario analyses.

Table 17: Variables Varied in Scenario Analyses

Scenario	Parameter	Reference case	Reference	Scenario analysis	Reference
1: Lower ICGFI capital cost per surgery (50% that of the reference case)	ICGFI capital cost per surgery	$194.00	Calculated	$97.00	Assumption
2: Higher ICGFI capital cost per surgery (assumed ICGFI use in 50% of colorectal surgeries at hospitals with ICGFI systems)	ICGFI capital cost per surgery	$194.00	Assumption	$388.00	Assumption
3: Higher annual maintenance cost for an ICGFI system (125% that of the reference case)	Annual maintenance cost for near-infrared imaging system	$18,500.00	Stryker Canada, email communication, May 22, 2024	$23,125.00	Assumption
4: Each vial of ICG dye portioned for 3 uses	Cost of ICG dye per surgery	$215.00	Stryker Canada, email communication, May 22, 2024	$71.67	Assumption
5: Lower cost of both ICGFI system and ICG dye (85% of list price)	Acquisition cost of ICGFI system	$250,000.00	Stryker Canada, email communication, May 22, 2024	$212,500.00	Assumption
5: Lower cost of both ICGFI system and ICG dye (85% of list price)	Cost of ICG dye	$215.00	Stryker Canada, email communication, May 22, 2024	$182.75	Assumption
6: 3% discount rate applied to both costs and QALYs	Discount rate	1.5%	CDA guidelines[66]	3%	Centre for Clinical Epidemiology and Evaluation[19]
7: 0% discount rate applied to both costs and QALYs	Discount rate	1.5%	CDA guidelines[66]	0%	CDA guidelines[66]
8: Baseline risk of AL for ileocolic anastomoses	Baseline risk of AL	0.0975	Median of range reported in literature[1]	0.0795	Median of range reported in literature[1]
9: Baseline risk of AL for colorectal anastomoses	Baseline risk of AL	0.0975	Median of range reported in literature[1]	0.0925	Median of range reported in literature[1]
10: Baseline risk of AL for coloanal anastomoses	Baseline risk of AL	0.0975	Median of range reported in literature[1]	0.12	Median of range reported in literature[1]

Abbreviations: AL, anastomotic leak; CDA, Canada's Drug Agency; ICG, indocyanine green; ICGFI, indocyanine green fluorescence imaging; QALY, quality-adjusted life-year.

Results

Reference Case Analysis

Table 18 provides the results of our reference case analysis. The mean total costs for the standard care and ICGFI treatment strategies were $4,447 and $3,023, respectively.

The mean total effect was 14.54 QALYs for ICGFI and 14.47 QALYs for standard care. The use of ICGFI resulted in a small average increase of 0.07 QALYs versus standard care over the duration of the model. While these results were quite similar, we identified greater differences in the mean total number of major ALs per 1,000 patients under each strategy: 31.3 for ICGFI and 53.4 for standard care. Using ICGFI

could thus prevent 22.1 major ALs per 1,000 patients undergoing colorectal surgery. The NNT is approximately 45, meaning that to prevent an additional major AL compared with standard care, around 45 people need to be treated.

Overall, compared with standard care, ICGFI was the dominant strategy, meaning that it is less costly and more effective.

Table 18: Reference Case Analysis Results

Strategy	Average total cost, $ (95% CrI)	Incremental cost, $ (95% CrI)[a,b]	Average total number of major ALs per 1,000 patients (95% CrI)	Average total number of major ALs avoided per 1,000 patients (95% CrI)	NNT to prevent an additional major AL (95% CrI)	Average total QALYs (95% CrI)	Incremental QALYs[c] (95% CrI)	ICER
Standard care	4,447 (3,550, 5,508)	–	53.4 (49.9, 56.8)	–	–	14.47 (6.64, 20.88)	–	–
ICGFI	3,023 (2,299, 3,937)	−1,424 (−1,251, −1,571)	31.3 (24.8, 39.2)	22.1 (25.1, 17.6)	45.25 (39.84, 56.82)	14.54 (6.67, 20.95)	0.07 (0.03, 0.07)	Dominated[d]

Abbreviations: AL, anastomotic leak; CrI, credible interval; ICER, incremental cost-effectiveness ratio; ICGFI, indocyanine green fluorescence imaging; NNT, number needed to treat; QALY, quality-adjusted life-year.

[a]Incremental cost = average cost (strategy B) − average cost (strategy A).

[b]Negative costs indicate savings.

[c]Incremental effect = average effect (strategy B) − average effect (strategy A).

[d]ICGFI was less costly and more effective than standard care.

In the vast majority of simulations for the probabilistic analysis, ICGFI generated more QALYs and lower costs than standard care (Figure 6).

When the results of the probabilistic analysis were plotted in a cost-effectiveness acceptability curve (Figure 7), we found that at the commonly used WTP values of $50,000 and $100,000 per QALY, the probability of ICGFI being cost-effective was 100%, that is, highly likely to be cost-effective.

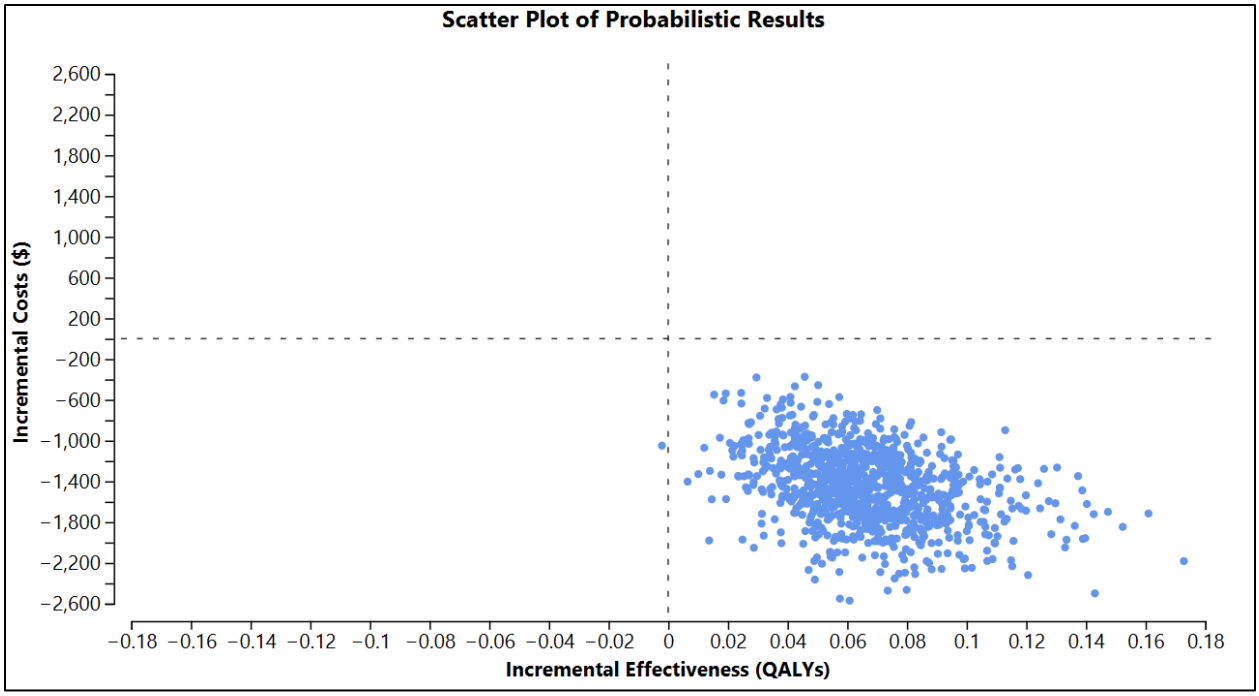

Figure 6: Scatter Plot of Probabilistic Results

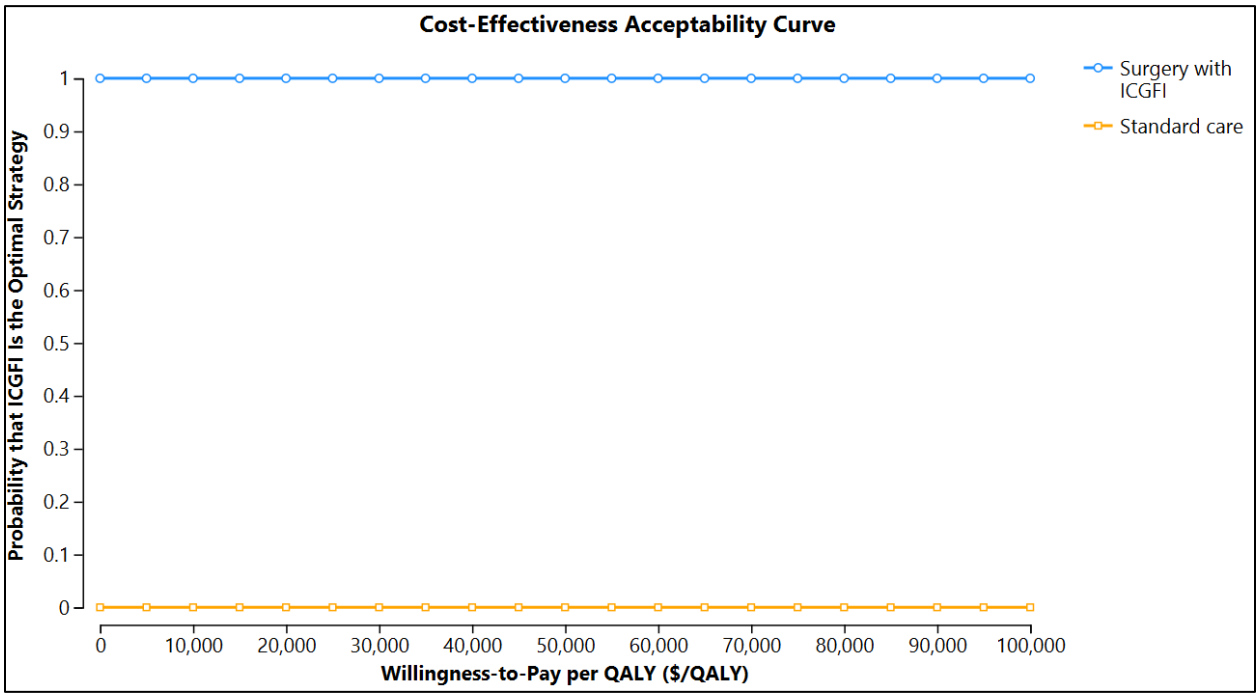

Figure 7: Cost-Effectiveness Acceptability Curve

Scenario Analysis

Across the 10 scenario analyses we conducted, ICGFI was the dominant strategy (more effective and less costly) compared with standard care (Table 19).

Overall, we found that lower costs associated with ICGFI (in scenarios 1, 4, and 5) resulted in greater cost savings (between an additional $50 and $144 in cost savings per person) compared with the reference case. In contrast, higher costs associated with ICGFI (in scenarios 2 and 3) resulted in smaller cost savings (a reduced cost savings of $19 [scenario 2] and $190 [scenario 3] per person) compared with the reference case.

Varying the baseline risk of AL affected the results of our reference case more than varying the cost of ICGFI components. Scenario 8, which assumed a lower baseline risk of AL, resulted in a greater reduction in cost savings ($339 less in cost savings per person) than the reference case. This finding also coincided with a lower average total number of major ALs avoided (18 per 1,000 patients) and a higher NNT (55.56) compared with the reference case.

On the other hand, scenario 10, which assumed a higher baseline risk of AL, resulted in considerably more cost savings ($424 more in cost savings per person) than the reference case. This finding also coincided with a higher average total number of major ALs avoided (27.1 per 1,000 patients) and a lower NNT (36.9) compared with the reference case. As expected, scenario 9, which assumed a similar baseline risk of AL, resulted in cost savings similar to those in the reference case. Our reference case results also remained relatively unchanged when discount rates of 3% and 0% were applied to both costs and effectiveness outcomes (QALYs) in scenarios 6 and 7, respectively.

We also ran 3 threshold analyses to determine when ICGFI would no longer be cost-saving and found this to be the case when:

- The cost of ICGFI (capital cost + cost of ICG dye) was $1,843 per surgery (compared with $409 per surgery in the reference case), or
- The additional hospitalization cost associated with treating a major AL was $7,625 (compared with $74,213 in the reference case), or
- The risk of an AL was only 9.2% lower with ICGFI compared with standard care (compared with a 42% lower risk in the reference case)

Table 19: Scenario Analysis Results

Strategy	Average total costs, $	Incremental cost, $[a,b]	Average total QALYs	Incremental QALYs[c]	Average total number of major ALs per 1,000 patients	Average total number of major ALs avoided per 1,000 patients	NNT to prevent an additional major AL	ICER
Reference case	SC: 4,447 ICGFI: 3,023	−1,424	SC: 14.47 ICGFI: 14.54	0.07	SC: 53.4 ICGFI: 31.3	22.1	45.25	Dominated[d]
Scenario 1: Lower ICGFI capital cost per surgery	SC: 4,447 ICGFI: 2,923	−1,525	SC: 14.47 ICGFI: 14.54	0.07	SC: 53.4 ICGFI: 31.3	22.1	45.25	Dominated[d]
Scenario 2: Higher ICGFI capital cost per surgery	SC: 4,447 ICGFI: 3,214	−1,234	SC: 14.47 ICGFI: 14.54	0.07	SC: 53.4 ICGFI: 31.3	22.1	45.25	Dominated[d]
Scenario 3: Higher annual maintenance cost for an ICGFI system	SC: 4,447 ICGFI: 3,042	−1,405	SC: 14.47 ICGFI: 14.54	0.07	SC: 53.4 ICGFI: 31.3	22.1	45.25	Dominated[d]
Scenario 4: Each vial of ICG dye portioned for 3 uses	SC: 4,447 ICGFI: 2,879	−1,568	SC: 14.47 ICGFI: 14.54	0.07	SC: 53.4 ICGFI: 31.3	22.1	45.25	Dominated[d]
Scenario 5: Lower cost of both ICGFI system and ICG dye	SC: 4,447 ICGFI: 2,972	−1,474	SC: 14.47 ICGFI: 14.54	0.07	SC: 53.4 ICGFI: 31.3	22.1	45.25	Dominated[d]
Scenario 6: 3% discount rate applied to both costs and QALYs	SC: 4,374 ICGFI: 2,980	−1,394	SC: 12.20 ICGFI: 12.26	0.06	SC: 53.4 ICGFI: 31.3	22.1	45.25	Dominated[d]
Scenario 7: 0% discount rate applied to both costs and QALYs	SC: 4,546 ICGFI: 3,081	−1,465	SC: 17.54 ICGFI: 17.62	0.08	SC: 53.4 ICGFI: 31.3	22.1	45.25	Dominated[d]
Scenario 8: Baseline risk of AL for ileocolic anastomoses	SC: 3,626 ICGFI: 2,541	−1,085	SC: 14.50 ICGFI: 14.55	0.05	SC: 43.5 ICGFI: 25.5	18	55.56	Dominated[d]
Scenario 9: Baseline risk of AL for colorectal anastomoses	SC: 4,219 ICGFI: 2,889	−1,330	SC: 14.48 ICGFI: 14.54	0.06	SC: 50.6 ICGFI: 29.7	20.9	47.85	Dominated[d]
Scenario 10: Baseline risk for AL for coloanal anastomoses	SC: 5,473 ICGFI: 3,625	−1,848	SC: 14.43 ICGFI: 14.52	0.08	SC: 65.7 ICGFI: 38.6	27.1	36.9	Dominated[d]

Abbreviations: AL, anastomotic leak; ICER, incremental cost-effectiveness ratio; ICG, indocyanine green; ICGFI, indocyanine green fluorescence imaging; NNT, number needed to treat; QALY, quality-adjusted life-year; SC, standard care.

[a]Incremental cost = average cost (strategy B) − average cost (strategy A).

[b]Negative costs indicate savings.

[c]Incremental effect = average effect (strategy B) − average effect (strategy A).

[d]ICGFI was less costly and more effective than standard care.

Discussion

Our reference case showed that despite ICGFI being associated with higher upfront costs than standard care (i.e., visual assessment alone), the overall cost of using ICGFI to assess anastomotic perfusion during colorectal surgery was completely offset by the savings associated with avoiding major (ISREC grade C) ALs. Moreover, the use of ICGFI generated a mean savings of $1,424 per patient.

Notably, while the use of ICGFI resulted in only a small average increase in QALYs (0.07 QALYs over a lifetime time horizon) compared with standard care, the difference in mean total number of major ALs under each strategy were greater. With ICGFI, around 22 major ALs per 1,000 patients could be avoided. This result was expected because, while a major AL is associated with a utility decrement, the negative impact of this major complication on health-related quality-of-life outcomes occurs only over a short time period, that is, until the leak is surgically treated. Further, the small average increase in QALYs between the 2 strategies suggests that while the use of ICGFI may prevent a considerable number of ALs, it does not have a downstream effect on overall mortality. This finding aligns with our clinical evidence review, which concluded that the effect of ICGFI on mortality is very uncertain (GRADE: Very low) and that there were no statistically significant differences in mortality found in the 4 included studies that conducted statistical analysis on this outcome.[37,39,48,49]

However, a major AL is associated with additional physician and hospital costs. Moreover, a patient with a major leak may require an ostomy and thus receive either a temporary or permanent stoma during reoperation to correct the leak. As such, when a major AL is avoided, these substantial costs are also avoided.

While ICGFI remained the dominant strategy throughout our 10 scenario analyses, we found that varying the baseline risk of AL affected the results of our reference case more than varying any other parameter. While we used the median of incidence of ALs reported for 3 sites of anastomosis (i.e., ileocolic, colorectal, and coloanal), the results of these 3 scenario analyses should not be interpreted as, or used to compare, the cost-effectiveness of ICGFI by site of anastomosis. This is because the incidence of ALs in the published literature ranges too widely to determine a meaningful estimate for each site of anastomosis. However, what can be concluded is that the higher the baseline risk of AL, the more cost savings ICGFI can generate by preventing a greater number of major ALs compared with standard care.

Our threshold analyses showed that ICGFI is no longer cost-saving only in 3 scenarios: (1) when the cost per surgery using ICGFI is 4.5 times more than our best estimate; (2) when the average additional hospitalization cost associated with treating a major AL is only one-tenth the cost of that in our reference case; or (3) when the risk of having an AL with ICGFI is more than 30% higher than what is reported in the findings of our clinical evidence review.

Overall, our reference case results remained robust throughout our probabilistic analysis and scenario analyses. Our finding that ICGFI is dominant (i.e., more effective and less costly) or cost-saving compared with standard care is consistent with those of the studies included in our economic evidence review.[19,61]

Equity Considerations

We expect that using ICGFI to assess anastomotic perfusion during colorectal surgery will occur primarily at hospitals performing high volumes of colorectal surgeries. This is because of the considerable capital investment required to incorporate the use of ICGFI in hospitals. The overall cost associated with ICGFI use is therefore volume dependent. Specifically, the capital cost of ICGFI per surgery decreases as

surgical volume increases. Because high-volume hospitals are typically located in large cities, patients who reside in remote or rural regions of Ontario may incur additional out-of-pocket costs to access a hospital that uses ICGFI for colorectal surgery.

Strengths and Limitations

Our primary economic evaluation provides comprehensive cost-effectiveness analyses of ICGFI versus standard care for the assessment of anastomotic perfusion during colorectal surgery from the perspective of the Ontario Ministry of Health. We leveraged previous work by adapting the economic model used in a report by British Columbia's Centre for Clinical Epidemiology and Evaluation,[19] making minor adjustments to reflect the most recent evidence and the Ontario context.

To ensure that the evidence used was of high quality, we derived our key clinical parameter from our clinical evidence review, which quantitively synthesized the effect of using ICGFI on the risk of AL. This synthesis was up to date and included the most recently published studies at the time of writing. Moreover, the clinical systematic review included both randomized controlled trials and nonrandomized studies, allowing the findings of the 2 types of studies to complement each other and allowing us to capture the best available evidence.

We also obtained local cost parameter inputs that best reflect actual expenditures in Ontario. For instance, we obtained all relevant procedure and hospitalization costs from local datasets generated from CIHI health administrative databases, the CIHI Patient Cost Estimator tool,[87] and the most up-to-date OHIP Schedule of Benefits for Physician Services.[86] Further, we obtained the most recent list prices of ICGFI components for Ontario directly from a manufacturer of ICGFI systems.

Some limitations to our analyses should be noted. First, we found few studies reporting utilities for minor and major ALs following colorectal surgery. As such, for minor ALs, we applied an arbitrary value of −0.02. This utility decrement was used in previous literature[19,83] to reflect the disutility of having a minor complication associated with colorectal surgery. For major ALs, we applied a utility value of 0.50, associated with experiencing pain and complications following colorectal surgery,[82] as a proxy for this event. The methods of utility elicitation for these 2 utility estimates are not consistent with the method of elicitation (i.e., the EQ-5D) used to generate all other utility parameters in our model. However, because these utility estimates were applied only in the first cycle (i.e., the first year) of our Markov model, any variations in these parameters are unlikely to substantially affect our reference case results. Moreover, both these utility sources were used in the Centre for Clinical Epidemiology and Evaluation report.[19]

Second, we conducted our cost-effectiveness analysis from the perspective of the Ontario Ministry of Health. As such, our analysis did not consider the costs of home care, time off work, productivity loss, or informal caregiver assistance associated with reoperation to correct an AL, nor did we account for any out-of-pocket costs that patients may incur. For instance, we based our estimate of the annual cost of ostomy supplies for a person with a permanent stoma on the amount covered by Ontario's Assistive Devices Program for these supplies ($975).[88] But the actual cost may be higher; some advocacy groups have reported that the annual cost of these supplies may be closer to $2,500.[94] We also did not account for the cost of ostomy supplies for temporary stomas as these are not publicly funded.

It should also be noted that for simplicity, our model does not capture all short- and long-term costs or outcomes associated with AL. For instance, on average, patients with either a minor or major (ISREC

grade B or C) AL have been found to spend around a week longer in the hospital following the index surgery compared with those without an AL.[95] Further, an AL can continue to affect a patient's functioning and quality of life even after it has been corrected; for example, they may experience compromised bowel, pelvic floor, and sphincter function.[1,96] Thus, our analysis may underestimate the full benefit of avoiding both minor and major ALs.

Finally, a main driver of our cost-effectiveness analyses was the effect of the use of ICGFI on risk of AL. Our clinical evidence review found that ICGFI showed promise for reducing ALs but noted some limitations in the body of evidence.

Conclusions

Our cost-effectiveness analysis showed that compared with standard care, ICGFI generated 0.07 additional QALYs, prevented 22 major ALs per 1,000 patients undergoing colorectal surgery, and was on average less costly by $1,424. With ICGFI, the NNT to prevent an additional major AL was approximately 45. Overall, ICGFI was dominant compared with standard care over a lifetime time horizon.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding indocyanine green fluorescence imaging (ICGFI) for the visualization of anastomotic perfusion during colorectal surgery?

Methods

Analytic Framework

We estimated the budget impact of publicly funding ICGFI for the visualization of anastomotic perfusion during colorectal surgery using the cost difference between 2 scenarios: (1) current clinical practice without public funding for ICGFI (the current scenario), and (2) anticipated clinical practice with public funding for ICGFI (the new scenario). Figure 8 presents the model schematic.

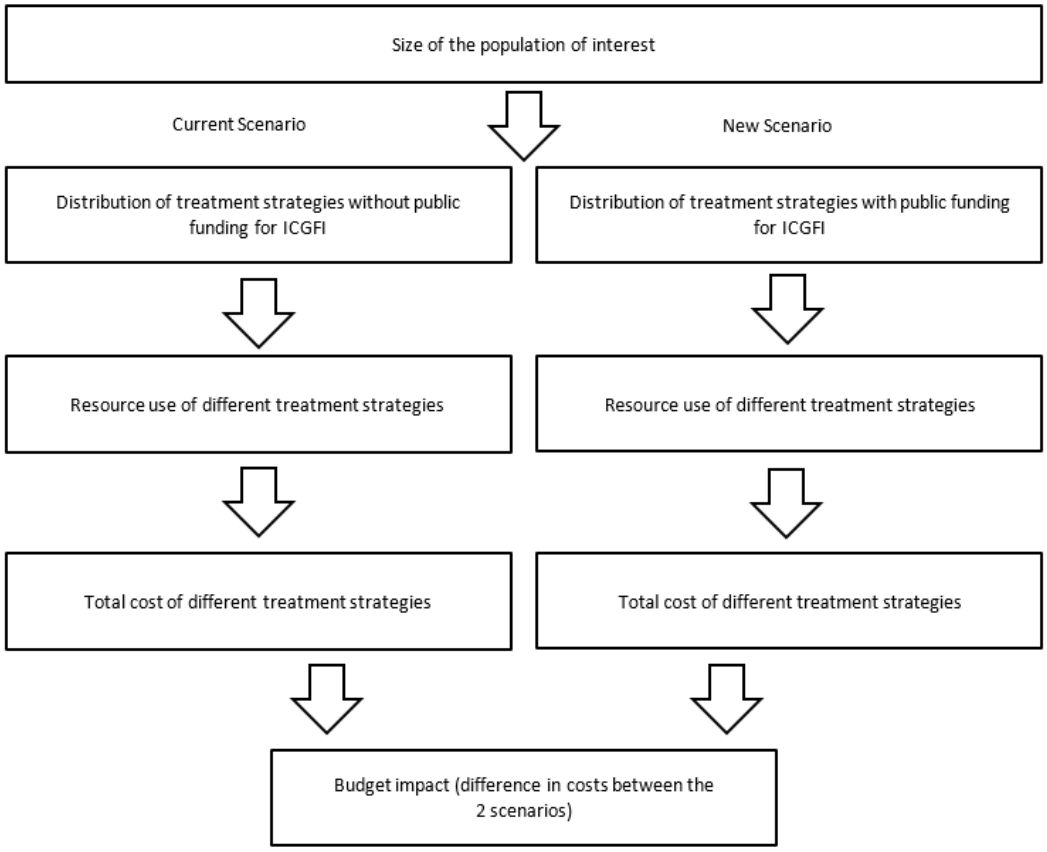

Figure 8: Schematic Model of Budget Impact

Abbreviation: ICGFI, indocyanine green fluorescence imaging
Flow chart describing the model for the budget impact analysis. Based on the size of the population of interest, we created 2 scenarios: the current scenario, which would explore the distribution of treatment strategies, resource use, and total costs without public funding for ICGFI and the new scenario, which would explore the distribution of treatment strategies, resource use, and total costs with public funding for ICGFI. The budget impact would represent the difference in costs between the 2 scenarios.

Key Assumptions

The main assumptions in our budget impact analysis include those used in our primary economic evaluation, plus the following:

- We estimated the size of our population of interest based on the average annual volume of colorectal surgeries with anastomosis performed in hospitals across Ontario from 2021 through 2023 (Appendix 6, Table A7). We assumed that the mean total number of colorectal surgeries with anastomosis performed during these years best reflects the capacity of the health care system to perform these surgeries in the post-COVID-19 period.
- In the current scenario, we assumed that several hospitals in Ontario are currently using ICGFI during colorectal surgeries with anastomosis.
    - We further assumed that these hospitals use ICGFI in 50% of the colorectal surgeries with anastomosis they perform. This assumption considers that the hospitals currently using ICGFI in these surgeries are doing so selectively due to cost (D. Abramowitz, MD, telephone communication, November 8, 2023; U. Hameed, MD, written communication, May 12, 2024).
- We assumed that if publicly funded, ICGFI would be used primarily in hospitals performing high volumes of colorectal resection surgeries because the capital cost per surgery for ICGFI is volume dependent.
- For simplicity, in our reference case, we assumed that the annual number of people undergoing colorectal surgery for malignant or benign conditions in Ontario will remain constant over the next 5 years. However, in a scenario analysis (scenario 7), we considered an annual increase in the number of surgeries performed.

Population of Interest

Our population of interest was adults (aged 18 years and older) undergoing colorectal surgery for malignant or benign conditions, including colorectal cancer, diverticulitis, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), and bowel obstruction, in Ontario. We estimated the size of this population using the methodology described in our primary economic evaluation (see Cost Parameters, above, for further details). Based on our dataset, we estimated that on average, a total of 7,561 colorectal surgeries with anastomosis are performed in Ontario each year (Appendix 6, Table A7).

Current Intervention Mix

In the current scenario, we considered that several hospitals in Ontario are currently using ICGFI to assess anastomotic perfusion during colorectal surgery.

Using the methodology described in our primary economic evaluation (see Cost Parameters, above, for further details), we estimated the average annual number of colorectal surgeries with anastomosis performed with ICGFI in the current scenario by (1) obtaining the average annual volume of colorectal surgeries with anastomosis conducted at these hospitals in 2021, 2022, and 2023, and (2) applying our assumption that 50% of these surgeries use ICGFI to assess anastomotic perfusion (D. Abramowitz, MD, telephone communication, November 8, 2023; U. Hameed, MD, written communication, May 12, 2024).

We estimated that in total, these hospitals performed an average of 863 colorectal surgeries with anastomosis using ICGFI each year.

We assumed that the remaining volume of colorectal surgeries with anastomosis performed in the province are conducted using standard care (i.e., visual assessment alone). Based on this assumption, we estimated that under the current scenario, around 6,697 colorectal resection surgeries are performed using visual assessment alone each year.

Uptake of the New Intervention and New Intervention Mix

The uptake of ICGFI depends on hospitals' acquisition of near-infrared imaging systems. We therefore assumed that the hospitals that already have a system would increase the percentage of colorectal surgeries with anastomosis performed using ICGFI to 100% in year 1 under the new scenario. This corresponds to an uptake rate of approximately 20% in year 1.

We then assumed that if publicly funded, ICGFI use would occur primarily in hospitals performing high volumes of colorectal resection surgeries because the capital cost per surgery for ICGFI is volume dependent. Using our previously generated dataset, we used the median of hospitals' annual volumes of colorectal surgeries with anastomosis as a cutoff point to categorize high-volume and low-volume hospitals. Using this cutoff point, we estimated that overall, high-volume hospitals perform approximately 85% of all colorectal resection surgeries in Ontario. Last, we assumed that uptake would increase by 10% in year 2, 15% in year 3, and 20% in year 4, for a total uptake rate of 85% by year 5.

These assumptions consider both the time required for a hospital to acquire a near-infrared imaging system and the time required for hospitals that previously did not have such a system to begin integrating ICGFI into their surgeries. Although it does not take a substantial amount of time for a surgical team to be trained on the use of ICGFI, it does take some time for teams to integrate ICGFI into their surgical procedures and develop comfort with the technology.

Table 20 provides the estimated number of colorectal surgeries with anastomosis performed in Ontario using standard care and ICGFI in the current scenario and our projected estimate of the use of ICGFI in Ontario over the next 5 years in the new scenario (i.e., with public funding for ICGFI).

Table 20: Estimated Number of Colorectal Surgeries Performed With Standard Care and ICGFI in the Current and New Scenarios

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Standard care, n	6,697	6,697	6,697	6,697	6,697	33,483
ICGFI, n	863	863	863	863	863	4,317
Total volume, n	7,560	7,560	7,560	7,560	7,560	37,800
New scenario[a]						
Uptake rate for ICGFI, %	20	30	45	65	85	
Standard care, n	6,048	5,292	4,158	2,646	1,134	19,278
ICGFI, n	1,512	2,268	3,402	4,914	6,426	18,522
Total volume, n	7,560	7,560	7,560	7,560	7,560	37,800

Abbreviation: ICGFI, indocyanine green fluorescence imaging.

[a]The volume of interventions was calculated from the total number multiplied by the uptake rate of the new intervention (i.e., ICGFI). For example, in the new scenario in year 1, the total volume is 7,560, and the ICGFI uptake rate is 20%, so the volume of surgeries performed with ICGFI in year 1 is 1,512 (7,560 × 20%).

Resources and Costs

We included all health care costs in our budget impact analysis by running the companion cost-effectiveness analysis previously described over the time horizon of the budget impact analysis (without discounting) to obtain the relevant costs. We also included disaggregated costs by key cost categories.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

We examined the following scenarios in our sensitivity analyses:

- Scenario 1: Assumed a lower capital cost per surgery using ICGFI (50% of that in the reference case).
- Scenario 2: Assumed a higher capital cost per surgery using ICGFI (2 times that of the reference case).
- Scenario 3: Assumed a higher (125%) annual maintenance cost for a near-infrared imaging system.
- Scenario 4: Assumed each vial of ICG dye is portioned for 3 uses.
- Scenario 5: Assumed a lower (85%) cost of both the near-infrared imaging system and the ICG dye.

- Scenario 6: Assumed a higher and more constant annual increase in the ICGFI uptake rate (16.35%) each year beginning in year 2. This scenario assumes an uptake rate of 20% in year 1, 36.25% in year 2, 52.50% in year 3, 68.75% in year 4, and 85% in year 5.
- Scenario 7: Assumed an annual increase (2.6%) in the total mean number of colorectal surgeries with anastomosis projected to be performed in Ontario over the next 5 years. This assumption is based on the projected incidence of colorectal cancer in Canada from 2023 to 2033.[97] Using the projected incidence for 2023 (n = 31,322) and 2033 (n = 40,510), and assuming a constant annual increase in incidence over those 10 years, we crudely calculated that the incidence will increase at an annual rate of 2.6%.
- Scenario 8: Applied the baseline risk of anastomotic leak (AL) for anastomoses created at the end of the ileum (at the end of the small intestine) and the beginning of the colon. For this scenario, we used the median (7.95%) of the range of incidence of ALs (1.6%–14.3%) reported in the literature for ileocolic anastomoses.[1]
- Scenario 9: Applied the baseline risk of AL for anastomoses involving the colon or the colon and rectum. For this scenario, we used the median (9.25%) of the range of incidence of ALs (0.5%–18%) reported in the literature for colorectal anastomoses.[1]
- Scenario 10: Applied the baseline risk of AL for anastomoses involving the colon and anus. For this scenario, we used the median (12%) of the range of incidence of ALs (5%–19%) reported in the literature for coloanal anastomoses.[1]

Results

Reference Case

Table 21 summarizes the total costs associated with using ICGFI to assess anastomotic perfusion during colorectal surgery in Ontario over the next 5 years. We found that the annual budget impact ranged from a cost savings of $0.81 million in year 1 to a cost savings of $8.13 million in year 5, for a total 5-year budget impact of $19.03 million in cost savings.

Opportunities for Cost Savings or a Reduction in Health Care Resource Use

While ICGFI is associated with an initial upfront cost to hospitals, it generates downstream savings by reducing the likelihood of patients having a major AL requiring reoperation and a lengthy hospital stay as compared with standard care. The savings were driven predominantly by the reduced number of hospitalizations needed for reoperation for major ALs (a savings of $0.87 million in year 1 and $7.48 million in year 5). However, these savings should not be interpreted as a net savings to the Ministry of Health's overall budget. Rather, they are cost reductions to portions of the Ministry of Health's budget and represent a release of system pressures (i.e., hospitalization resources), allowing hospitals to reallocate some resources to other areas.

If only the cost of ICGFI (i.e., the capital cost of ICGFI per surgery plus the cost of ICG dye per surgery) were considered, publicly funding ICGFI would increase the budget by $0.27 million in year 1 and $2.29 million in year 5, for a total of $5.85 million over the next 5 years.

Table 21: Budget Impact Analysis Results – Reference Case

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
Current scenario	29.40	29.57	29.74	29.91	31.15	149.77
Standard care	27.00	27.16	27.32	27.47	27.62	136.58
ICGFI (system)	0	0	0	0	0	0
Physician services	5.40	5.40	5.40	5.40	5.40	27.01
Hospitalization	21.83	21.83	21.83	21.83	21.83	109.13
Stoma supplies	0.34	0.50	0.66	0.82	0.97	3.29
Medication	0.03	0.03	0.03	0.03	0.03	0.16
ICGFI	2.40	2.41	2.42	2.44	3.53	13.20
ICGFI (system)	0.36	0.36	0.36	0.36	0.36	1.78
Physician services	0.41	0.41	0.41	0.41	0.41	2.04
Hospitalization	1.65	1.65	1.65	1.65	1.65	8.26
Stoma supplies	0.03	0.04	0.05	0.06	0.07	0.25
Medication	0.002	0.002	0.002	0.002	0.002	0.01
New scenario	28.58	27.81	26.54	24.79	23.02	130.74
Standard care	24.38	21.48	17.04	11.03	4.99	78.93
ICGFI (system)	0	0	0	0	0	0
Physician services	4.88	4.27	3.35	2.13	0.91	15.55
Hospitalization	19.71	17.25	13.55	8.62	3.70	62.83
Stoma supplies	0.31	0.42	0.48	0.50	0.48	2.19
Medication	0.030	0.026	0.020	0.000	0.01	0.08
ICGFI	4.20	6.32	9.51	13.76	18.02	51.81
ICGFI (system)	0.62	0.93	1.40	2.03	2.65	7.63
Physician services	0.72	1.07	1.61	2.33	3.04	8.76
Hospitalization	2.89	4.34	6.51	9.40	12.30	35.44
Stoma supplies	0.05	0.09	0.16	0.25	0.36	0.90
Medication	0.004	0.007	0.010	0.014	0.019	0.05
Budget impact[b,c]	−0.81	−1.77	−3.20	−5.12	−8.13	−19.03

Abbreviation: ICGFI, indocyanine green fluorescence imaging.

[a]In 2024 Canadian dollars.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding. All costs were calculated using the mean cost from the results of the probabilistic analysis reported in the primary economic evaluation.

Sensitivity Analysis

Table 22 summarizes the results of the 10 scenario analyses conducted for the budget impact analysis. Across all scenarios, publicly funding ICGFI generated cost savings for the province. Compared with the reference case, scenarios that considered a higher cost of ICGFI resulted in reduced cost savings. For instance, compared with the reference case, assuming a higher capital cost per surgery using ICGFI

(scenario 2) resulted in $2.97 million less in total cost savings, and a higher annual ICGFI maintenance cost (scenario 3) resulted in $0.29 million less in total cost savings.

In contrast, scenarios that considered a lower cost of ICGFI resulted in greater cost savings compared with the reference case. For instance, assuming a lower capital cost per surgery using ICGFI (scenario 1), a lower cost of ICG dye per surgery (scenario 4), and a lower cost of both near-infrared imaging system and ICG dye (scenario 5) resulted in $1.49 million, $2.16 million, and $0.76 million more in cost savings compared with the reference case, respectively. Greater cost savings were also found when there was a higher annual increase in the ICGFI uptake rate (an additional $0.61 million [scenario 6]) and when there was an annual increase in the volume of colorectal surgeries with anastomosis (an additional $0.61 million [scenario 7]).

Our scenario analyses also show that a lower baseline risk of AL was associated with reduced cost savings (scenario 8), whereas a higher baseline risk was associated with greater cost savings (scenario 10). As expected, our analysis of a baseline risk of AL similar to that in the reference case (scenario 9) resulted in cost savings similar to those of the reference case.

Table 22: Budget Impact Analysis Results – Scenario Analyses

	Budget impact, $ million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b,c]**
Reference case	−0.81	−1.77	−3.20	−5.12	−8.13	−19.03
Scenario 1: Lower ICGFI capital cost per surgery	−0.88	−1.90	−3.45	−5.52	−8.77	−20.52
Scenario 2: Higher ICGFI capital cost per surgery	−0.68	−1.49	−2.70	−4.32	−6.87	−16.06
Scenario 3: Higher annual maintenance cost for an ICGFI system	−0.80	−1.74	−3.15	−5.04	−8.01	−18.74
Scenario 4: Each vial of ICG dye is portioned for 3 uses	−0.91	−1.97	−3.56	−5.70	−9.06	−21.19
Scenario 5: Lower cost of both ICGFI system and ICG dye	−0.85	−1.84	−3.33	−5.32	−8.46	−19.79
Scenario 6: Higher and more constant annual increase in ICGFI uptake rate	−0.81	−2.36	−3.92	−5.49	−7.07	−19.64
Scenario 7: Annual increase in colorectal surgery volumes in Ontario	−0.81	−2.42	−2.52	−5.91	−7.82	−19.48
Scenario 8: Baseline risk of AL for ileocolic anastomoses	−0.61	−1.33	−2.42	−3.87	−6.14	−14.37
Scenario 9: Baseline risk of AL for colorectal anastomoses	−0.76	−1.65	−2.98	−4.77	−7.58	−17.74
Scenario 10: Baseline risk of AL for coloanal anastomoses	−1.06	−2.31	−4.18	−6.69	−10.62	−24.86

Abbreviations: AL, anastomotic leak; ICGFI, indocyanine green fluorescence imaging.

[a]In 2024 Canadian dollars.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding. All costs were calculated using the mean cost from the results of the probabilistic analysis reported in the primary economic evaluation.

Discussion

The use of ICGFI to assess anastomotic perfusion during colorectal surgeries is associated with upfront costs that are completely offset by the downstream savings associated with preventing major (ISREC grade C) ALs that require reoperation and hospitalization. Moreover, ICGFI generates additional cost savings associated with a reduction in hospital resource use and related costs.

Predominantly because of the substantial hospitalization costs associated with reoperation to correct an AL, ICGFI generated cost savings across all 10 scenario analyses that we conducted. As mentioned, these savings do not represent net savings to the Ministry of Health's overall budget but rather reduced pressure on hospitalization resources, allowing hospitals to reallocate some resources to other areas.

It is important to note that in addition to colorectal surgery, ICGFI is currently being used in Ontario to assess tissue perfusion in a variety of other surgical procedures, including plastics reconstructive surgery, hepatobiliary surgery for open liver resections, transplant surgeries, coronary bypass, renal cancer surgeries, vascular surgeries, cardiac surgeries, and endocrine surgeries (Stryker Canada, email communication, November 7, 2023). Because the capital cost per surgery of a near-infrared imaging system is volume dependent, this cost may be lower, depending on the use of ICGFI in current practice at Ontario hospitals, than the estimate we used for this cost parameter. To account for this possibility, we conducted a scenario analysis (scenario 1) that assumed a capital cost per surgery using ICGFI of 50% less than that used in our reference case. This scenario analysis found that ICGFI generated greater cost savings ($1.49 million) over the next 5 years as compared with the reference case.

Strengths and Limitations

We derived the estimates for our budget impact analysis by running our cost-effectiveness analysis, the key parameters of which were obtained from our clinical evidence review and from Canadian sources. Further, we validated our assumptions and estimates with clinical experts with expertise in the use of ICGFI, colorectal surgery, and surgical oncology.

We estimated the size of our population of interest based on a local dataset generated using a health administrative database maintained by the Canadian Institute for Health Information, which best reflects the actual volume of colorectal surgeries performed in Ontario. In our scenario analyses, we also accounted for the current diffusion of ICGFI in select high-volume hospitals in the province.

However, for the high-volume hospitals that do not currently have near-infrared imaging systems, it was difficult to determine which hospitals would acquire a system, how quickly they would do so, and how quickly their surgical teams would begin using ICGFI for all colorectal surgeries with anastomosis. As such, we relied on reasonable assumptions to estimate the uptake rate of ICGFI if it were publicly funded.

A final limitation is that we were unable to evaluate equity considerations in our budget impact analysis.

Conclusions

We estimate that publicly funding ICGFI to assess anastomotic perfusion in colorectal resection surgeries in Ontario would lead to an annual budget impact ranging from a cost savings of $0.81 million in year 1 to a cost savings of $8.13 million in year 5, for a total 5-year budget impact of $19.03 million in cost savings. Importantly, these savings represent a reduction in health care resource use (specifically

hospitalization resources) rather than net savings to the Ministry of Health's overall budget. As such, these savings would accrue to hospitals rather than to the Ministry of Health, as they are an estimate of the savings associated with a reduction in the use of hospitalization resources.

If only ICGFI costs are considered, publicly funding ICGFI would increase the budget by $0.27 million in year 1 and $2.29 million in year 5, for a total 5-year budget impact of $5.85 million.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of colorectal surgery, as well as the preferences and perceptions of patients regarding the use of indocyanine green fluorescence imaging (ICGFI) in colorectal surgery.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other care partners, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[98-100] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

The health technology assessment conducted by British Columbia's Centre for Clinical Epidemiology and Evaluation[19] (referred to earlier in this report) included a rapid review of qualitative studies conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH; now Canada's Drug Agency).[101] We leveraged the CADTH report, which evaluated the experiences of patients who had undergone colorectal cancer surgery.

Summary of the CADTH Rapid Review

CADTH conducted a rapid review of qualitative studies to address 3 research questions[101]:

7) What are the expectations and anticipated outcomes of patients regarding colorectal surgery for any indication?
8) What outcomes of colorectal surgery are identified as important or relevant from the perspective of postoperative patients?
9) What are the experiences and perspectives of patients regarding indocyanine green angiography (ICGA) for surgical procedures?

CADTH identified no literature on the patient experience of ICGA in colorectal surgery but identified 5 studies on the experience of patients who had undergone surgery for colorectal cancer. Key insights include the following:

Preoperative Expectations

- Core outcomes: Core outcomes were established through consensus between patients and providers and categorized into oncological outcomes, operative outcomes (e.g., anastomotic leak), and quality of life.
- Influence of cancer experience: A lack of previous experience with colorectal cancer influenced how patients understood surgical outcomes.

Postoperative Experiences

- Information gaps: Many patients reported receiving insufficient information about surgical outcomes.
- Anxiety and fear: Patients expressed worries about future health, cancer recurrence, and the impact of treatment on their lives. Some reported continued fear despite having undergone successful treatment.

Direct Patient Engagement

For this health technology assessment, Ontario Health's Patient and Public Partnering team determined the scope and direction of patient and public engagement using a formal needs assessment. The purpose of this needs assessment was threefold:

- To determine whether obtaining lived-experience information about ICGFI would be of value in understanding the impact of this technology
- If lived-experience information was determined to be of value, to determine the goals and objectives for patient engagement to obtain this information
- To scope the optimal engagement activity

To complete the needs assessment, we conducted background research on the topic in question, which included reviewing the clinical review plan and consulting with clinical experts. As we refined the needs assessment, we also consulted with lived-experience advisors on the Ontario Health Technology Advisory Committee.

Following the completion of our needs assessment and consultations, we determined that lived-experience information would not be needed to evaluate the impact of ICGFI for several reasons:

- Patient preferences and values in decision-making: For health technology assessment, patient engagement can often illuminate patient preferences related to a technology and how patients make decisions regarding its use in their care. However, we determined that it was unlikely that patient preferences regarding ICGFI would affect whether the technology would be used because clinical experts reported that patients currently have no direct influence on decision-making regarding the use of this technology in their care.

- Direct effect on patients: Many health technology assessments evaluate devices or procedures that directly affect a patient's physical state. For example, a device may be inserted or worn, or a procedure may be performed that causes or relieves symptoms. Direct patient engagement to determine patient preferences and values for such devices and procedures can provide insight into, for example, the outcomes most desired by patients and how patients make decisions about their care. However, ICGFI is not a technology managed by patients or integrated into their daily life. Its purpose is to enhance visualization of the surgical area, and it is the surgeon alone who determines whether to use the technology. Because of this, the types of insights into patient preferences and values that can provide valuable information for decision-making regarding the use of certain health technologies—such as how a technology feels to use or wear or how it affects a person's quality of life—were not relevant to this health technology assessment.
- Patient outcomes: A key component of health technology assessment is evaluating the impact of a technology on important patient outcomes. In many cases, direct patient engagement can provide valuable information about which outcomes are most important and relevant to patients. In our needs assessment and CADTH's report,[101] the outcome of anastomotic leak was identified as being important to patients. Since the clinical evidence review of this health technology assessment evaluated that outcome, as well as other patient-important outcomes including readmission, reoperation, sepsis, length of hospital stay, mortality, and quality of life, we determined that direct patient engagement would not provide further relevant evidence.

After careful consideration of these factors and following a needs assessment and consultation with lived-experience advisors, the Ontario Health Patient and Public Partnering team concluded that direct patient engagement would not provide additional evidence to guide the decision-making of the Ontario Health Technology Advisory Committee.

Preferences and Values Evidence Conclusions

A previously published rapid review evaluating the experiences of patients who had undergone colorectal cancer surgery found no qualitative literature on the patient experience of ICGFI; however, qualitative studies identified anastomotic leak and quality of life as key patient-important outcomes. In the included studies, patients often reported not receiving enough information about surgical outcomes and anxiety regarding cancer recurrence. We did not engage directly with patients for this report because we determined that it was unlikely that patient preferences regarding the use of ICGFI would affect whether the technology is used by surgeons to enhance visualization of the surgical area. Further, we expected that patients' preferences and values would align with the potential for improved health outcomes from the use of this technology.

Conclusions of the Health Technology Assessment

Compared with visual assessment alone, the addition of indocyanine green fluorescence imaging (ICGFI) to assess anastomotic perfusion during colorectal surgery reduces anastomotic leaks (GRADE: Low) and reoperations (GRADE: Low). It also slightly reduces sepsis, but the evidence is very uncertain (GRADE: Very low to Low). ICGFI appears to have little to no effect on hospital readmission (GRADE: Low) or length of stay (GRADE: Low to Moderate), and its effect on mortality is very uncertain (GRADE: Very low). None of the included studies provided data on the outcome of quality of life.

Our primary economic evaluation found that compared with visual assessment alone, the addition of ICGFI to assess anastomotic perfusion during colorectal surgery generated 0.07 additional quality-adjusted life-years (QALYs) and was less costly by $1,424 over a lifetime time horizon. Compared with visual assessment alone, ICGFI is highly likely to be cost-effective at the commonly used willingness-to-pay values of $50,000 and $100,000 per QALY. The use of ICGFI could prevent 22 major anastomotic leaks per 1,000 patients undergoing colorectal surgery. With ICGFI, 45 patients would need to be treated to prevent an additional major anastomotic leak. We estimate that publicly funding ICGFI to assess anastomotic perfusion during colorectal surgery in Ontario would lead to cost savings of $19.03 million over the next 5 years.

A previously published rapid review evaluating the experiences of patients who had undergone colorectal cancer surgery found no qualitative literature on the patient experience of ICGFI; however, qualitative studies identified anastomotic leak and quality of life as key patient-important outcomes. In the included studies, patients often reported not receiving enough information about surgical outcomes and anxiety regarding cancer recurrence. We did not engage directly with patients for this report because we determined that it was unlikely that patient preferences regarding the use of ICGFI would affect whether the technology is used by surgeons to enhance visualization of the surgical area. Further, we expected that patients' preferences and values would align with the potential for improved health outcomes from the use of this technology.

Abbreviations

ACS-NSQIP: American College of Surgeons National Safety and Quality Improvement Program

AL: anastomotic leak

ASA: American Society of Anesthesiologists

CADTH: Canadian Agency for Drugs and Technologies in Health

CCI: Canadian Classification of Health Intervention

CDA: Canada's Drug Agency

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CI: confidence interval

CIHI: Canadian Institute for Health Information

CT: computerized tomography

DAD: Discharge Abstract Database

DSCA: Dutch Surgical Colorectal Audit

EAES: European Association of Endoscopic Surgery

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

HTA: health technology assessment

ICD: International Statistical Classification of Diseases and Related Health Problems

ICER: incremental cost-effectiveness ratio

ICG: indocyanine green

ICGFI: indocyanine green fluorescence imaging

IHCC: individual hospital capital cost

ISREC: International Study Group of Rectal Cancer

NICE: National Institute for Health and Care Excellence

NNT: number needed to treat

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

RCT: randomized controlled trial

RoBANS: Risk-of-Bias Assessment Tool for Nonrandomized Studies

RR: risk ratio

SD: standard deviation

WTP: willingness-to-pay

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Anastomosis: A surgical connection of the remaining healthy sections of the intestine after the affected part has been removed.[102]

Anastomotic leak: A serious potential complication of colorectal resection surgery that occurs when the contents of the bowel leak from the site of anastomosis.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cohort model: In economic evaluations, a cohort model is used to simulate what happens to a homogeneous cohort (group) of patients after receiving a specific health care intervention. The proportion of the cohort who experiences certain health outcomes or events is estimated, along with the relevant costs and benefits. In contrast, a microsimulation model follows the course of individual patients.

Colectomy: A surgery to remove part or all of the colon (large intestine) that may involve the creation of an anastomosis; also called a *colon resection surgery* or a *colorectal resection surgery*.[102]

Cost–consequence analysis: A cost–consequence analysis is a type of economic evaluation that estimates the costs and consequences (i.e., the health outcomes) of two or more health care interventions. In this type of analysis, the costs are presented separately from the consequences.

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used

more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Deterministic sensitivity analysis: Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Disutility: A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[103] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment

and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Health inequity: Health inequities are avoidable inequalities in health between groups of people within countries and between countries.[31] These inequities arise from inequalities within and between societies. Social and economic conditions and their effects on people's lives determine their risk of illness and the actions taken to prevent them becoming ill or treat illness when it occurs.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Markov model: A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Natural history of a disease: The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte

Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses involve varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Sex: biological sex assigned at birth.

Significant: Refers to statistical significance, a mathematical measure of difference between groups. The difference is said to be statistically significant if it is greater than what might be expected to happen by chance alone. Also; statistically significant.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay

value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: January 29, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 24, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 04>, Ovid MEDLINE(R) ALL <1946 to January 26, 2024>

Search strategy:

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1 Colectomy/ (25510)
2 (colectom* or hemicolectom* or sigmoidectom* or ileocolectom*).ti,ab,kf. (56404)
3 Colorectal Surgery/ (23859)
4 (((bowel* or colon* or colorectal* or colosigmoid* or colo sigmoid* or coloanal* or colo anal* or colocolon* or ileocolon* or ileo colon* or mesocol* or meso col* or rectal* or rectum* or rectosigmoid* or recto sigmoid* or rectalsigmoid* or mesorectal* or meso rectal* or intersphincteric* or inter* sphincteric*) adj3 (surg* or operat* or procedure* or excision* or resection* or re section* or recision* or dissection* or anastomo* or reattach* or re attach* or reconnect* or re connect* or removal*)) or rectosigmoidectom*).ti,ab,kf. (194381)
5 Proctectomy/ (10982)
6 (proctectom* or anterior resection*).ti,ab,kf. (21299)
7 or/1-6 (255010)
8 Anastomotic Leak/ (19963)
9 Anastomosis, Surgical/ (87061)
10 Perfusion Imaging/ (32063)
11 ((anastomo* adj3 perfusion*) or ((anastomo* or perfusion* or blood flow* assess*) adj6 (leak* or integrit* or excision* or resection* or re section* or recision* or dissection* or reattach* or re attach or reconnect* or re connect* or removal*))).ti,ab,kf. (63184)
12 or/8-11 (172123)
13 Colorectal Neoplasms/ (138552)
14 Colonic Neoplasms/ (92887)
15 Rectal Neoplasms/ (58698)
16 ((bowel* or colon* or colorectal* or colosigmoid* or colo sigmoid* or coloanal* or colo anal* or colocolon* or ileocolon* or ileo colon* or mesocol* or meso col* or rectal* or rectum* or rectosigmoid* or recto sigmoid* or mesorectal* or meso rectal* or intersphincteric* or inter* sphincteric) adj3 (adenocarcinoma* or cancer* or carcinogen* or carcinoma* or malignan* or metasta* or neoplasm* or oncolog* or tumo?r*)).ti,ab,kf. (734755)
17 exp Inflammatory Bowel Diseases/ (302534)

18 (inflam* adj3 bowel disease*).ti,ab,kf. (185202)
19 ((bowel adj3 obstruct*) or (ulcerat* adj3 colitis*) or idiopath* proctocolitis* or colitis* gravis* or familial adenomatous polypos* or lynch syndrome*).ti,ab,kf. (199867)
20 ((crohn* adj3 (disease* or enteritis*)) or colitis granulomat* or ileocolitis* or ileo colitis* or regional enteriti* or ((regional or terminal) adj3 ileiti*)).ti,ab,kf. (162005)
21 Diverticulitis/ (13555)
22 Diverticulitis, Colonic/ (8542)
23 diverticuliti*.ti,ab,kf. (19142)
24 or/13-23 (1200972)
25 12 and 24 (29796)
26 or/7,25 (262643)
27 Indocyanine Green/ (29579)
28 Fluorescein Angiography/ (56883)
29 indocyanin*.ti,ab,kf. (36626)
30 ((fluoresce* or green*) adj3 (angiograph* or intraluminal* or near infrared* or near infra red*)).ti,ab,kf. (53305)
31 (NIR adj3 fluoresce* imaging*).ti,ab,kf. (2537)
32 (green adj3 fluoresce*).ti,ab,kf. (106956)
33 ((intraoperat* or intra operat*) adj3 (angiograph* or fluoresce* or near infrared* or near infra red*)).ti,ab,kf. (7026)
34 (ICG or ICGA or ICGFA or ICGFI or ICGNIRF or ICYG or IGFA or NIR FI or NIRFI).ti,ab,kf. (26972)
35 (novadaq* or stryker* or (pinpoint* adj3 (fluoresce* or imag* or tower*)) or (spy* adj3 (elite* or angiograph* or fluoresce* or agent* or green* or imag* or portab* or handheld or tower*)) or SPY PHI* or SPYPHI* or SPY QP* or SPYQP*).ti,ab,kf. (4285)
36 ((rubina* or storz* or image1* or intuitive* or da vinci robot* or da vinci surg*) adj5 (fluoresce* or green* or near infrared* or near infra red* or NIR)).ti,ab,kf. (280)
37 (("1688" or "1788") adj3 (camera* or video* or 4k or spy* or imaging*)).ti,ab,kf. (16)
38 or/27-37 (228289)
39 26 and 38 (2179)
40 exp Animals/ not Humans/ (16441172)
41 39 not 40 (1900)
42 (Comment or Editorial or (Letter not (Letter and Randomized Controlled Trial)) or Congress).pt. (4359849)
43 41 not 42 (1781)
44 limit 43 to english language [Limit not valid in CDSR; records were retained] (1692)
45 44 use medall,coch,cctr,cleed (664)
46 exp colectomy/ (45864)
47 ileocolectomy/ (337)
48 (colectom* or hemicolectom* or sigmoidectom* or ileocolectom*).tw,kw,kf. (56600)
49 colorectal surgery/ (23859)
50 rectosigmoid resection/ (159)
51 colorectal anastomosis/ (2797)
52 rectum resection/ (10942)
53 (((bowel* or colon* or colorectal* or colosigmoid* or colo sigmoid* or coloanal* or colo anal* or colocolon* or ileocolon* or ileo colon* or mesocol* or meso col* or rectal* or rectum* or rectosigmoid* or recto sigmoid* or rectalsigmoid* or mesorectal* or meso rectal* or intersphincteric* or inter* sphincteric*) adj3 (surg* or operat* or procedure* or excision* or resection* or re section* or recision*

or dissection* or anastomo* or reattach* or re attach* or reconnect* or re connect* or removal*)) or rectosigmoidectom*).tw,kw,kf. (199999)
54 (proctectom* or anterior resection*).tw,kw,kf. (21350)
55 or/46-54 (268530)
56 anastomosis leakage/ (27508)
57 anastomosis/ (53256)
58 ((anastomo* adj3 perfusion*) or ((anastomo* or perfusion* or blood flow* assess*) adj6 (leak* or integrit* or excision* or resection* or re section* or recision* or dissection* or reattach* or re attach or reconnect* or re connect* or removal*))).tw,kw,kf. (63688)
59 or/56-58 (117806)
60 exp colorectal tumor/ (716480)
61 ((bowel* or colon* or colorectal* or colosigmoid* or colo sigmoid* or coloanal* or colo anal* or colocolon* or ileocolon* or ileo colon* or mesocol* or meso col* or rectal* or rectum* or rectosigmoid* or recto sigmoid* or mesorectal* or meso rectal* or intersphincteric* or inter* sphincteric) adj3 (adenocarcinoma* or cancer* or carcinogen* or carcinoma* or malignan* or metasta* or neoplasm* or oncolog* or tumo?r*)).tw,kw,kf. (738023)
62 exp inflammatory bowel disease/ (302534)
63 (inflam* adj3 bowel disease*).tw,kw,kf. (185631)
64 ((bowel adj3 obstruct*) or (ulcerat* adj3 colitis*) or idiopath* proctocolitis* or colitis* gravis* or familial adenomatous polypos* or lynch syndrome*).tw,kw,kf. (200403)
65 ((crohn* adj3 (disease* or enteritis*)) or colitis granulomat* or ileocolitis* or ileo colitis* or regional enteriti* or ((regional or terminal) adj3 ileiti*)).tw,kw,kf. (162399)
66 diverticulitis/ (13555)
67 colon diverticulosis/ (6629)
68 diverticuliti*.tw,kw,kf. (19227)
69 or/60-68 (1313014)
70 59 and 69 (28367)
71 or/55,70 (274690)
72 indocyanine green/ (29579)
73 indocyanine green angiography/ (6440)
74 fluorescence angiography/ (57160)
75 indocyanin*.tw,kw,kf,dv. (36680)
76 ((fluoresce* or green*) adj3 (angiograph* or intraluminal* or near infrared* or near infra red*)).tw,kw,kf,dv. (54138)
77 (NIR adj3 fluoresce* imaging*).tw,kw,kf,dv. (2545)
78 (green adj3 fluoresce*).tw,kw,kf,dv. (106978)
79 ((intraoperat* or intra operat*) adj3 (angiograph* or fluoresce* or near infrared* or near infra red*)).tw,kw,kf,dv. (7400)
80 (ICG or ICGA or ICGFA or ICGFI or ICGNIRF or ICYG or IGFA or NIR FI or NIRFI).tw,kw,kf,dv. (27177)
81 (novadaq* or stryker* or (pinpoint* adj3 (fluoresce* or imag* or tower*)) or (spy* adj3 (elite* or angiograph* or fluoresce* or agent* or green* or imag* or portab* or handheld or tower*)) or SPY PHI* or SPYPHI* or SPY QP* or SPYQP*).tw,kw,kf,dv. (10753)
82 ((rubina* or storz* or image1* or intuitive* or da vinci robot* or da vinci surg*) adj5 (fluoresce* or green* or near infrared* or near infra red* or NIR)).tw,kw,kf,dv. (294)
83 (("1688" or "1788") adj3 (camera* or video* or 4k or spy* or imaging*)).tw,kw,kf,dv. (19)
84 or/72-83 (236712)
85 71 and 84 (2248)
86 (exp animal/ or nonhuman/) not exp human/ (12034565)

87 85 not 86 (2151)
88 Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (9287888)
89 87 not 88 (1434)
90 limit 89 to english language [Limit not valid in CDSR; records were retained] (1336)
91 90 use emez (664)
92 45 or 91 (1328)
93 92 use medall (556)
94 92 use coch (0)
95 92 use cctr (108)
96 92 use cleed (0)
97 92 use emez (664)
98 remove duplicates from 92 (810)

Economic Evidence Search

Search Date: January 30, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 24, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 04>, Ovid MEDLINE(R) ALL <1946 to January 29, 2024>
Search Strategy:
---
1 Colectomy/ (25516)
2 (colectom* or hemicolectom* or sigmoidectom* or ileocolectom*).ti,ab,kf. (56409)
3 Colorectal Surgery/ (23861)
4 (((bowel* or colon* or colorectal* or colosigmoid* or colo sigmoid* or coloanal* or colo anal* or colocolon* or ileocolon* or ileo colon* or mesocol* or meso col* or rectal* or rectum* or rectosigmoid* or recto sigmoid* or rectalsigmoid* or mesorectal* or meso rectal* or intersphincteric* or inter* sphincteric*) adj3 (surg* or operat* or procedure* or excision* or resection* or re section* or recision* or dissection* or anastomo* or reattach* or re attach* or reconnect* or re connect* or removal*)) or rectosigmoidectom*).ti,ab,kf. (194404)
5 Proctectomy/ (10982)
6 (proctectom* or anterior resection*).ti,ab,kf. (21303)
7 or/1-6 (255037)
8 Anastomotic Leak/ (19966)
9 Anastomosis, Surgical/ (87067)
10 Perfusion Imaging/ (32064)
11 ((anastomo* adj3 perfusion*) or ((anastomo* or perfusion* or blood flow* assess*) adj6 (leak* or integrit* or excision* or resection* or re section* or recision* or dissection* or reattach* or re attach or reconnect* or re connect* or removal*))).ti,ab,kf. (63196)
12 or/8-11 (172141)
13 Colorectal Neoplasms/ (138629)

14 Colonic Neoplasms/ (92903)
15 Rectal Neoplasms/ (58712)
16 ((bowel* or colon* or colorectal* or colosigmoid* or colo sigmoid* or coloanal* or colo anal* or colocolon* or ileocolon* or ileo colon* or mesocol* or meso col* or rectal* or rectum* or rectosigmoid* or recto sigmoid* or mesorectal* or meso rectal* or intersphincteric* or inter* sphincteric) adj3 (adenocarcinoma* or cancer* or carcinogen* or carcinoma* or malignan* or metasta* or neoplasm* or oncolog* or tumo?r*)).ti,ab,kf. (734877)
17 exp Inflammatory Bowel Diseases/ (302610)
18 (inflam* adj3 bowel disease*).ti,ab,kf. (185256)
19 ((bowel adj3 obstruct*) or (ulcerat* adj3 colitis*) or idiopath* proctocolitis* or colitis* gravis* or familial adenomatous polypos* or lynch syndrome*).ti,ab,kf. (199907)
20 ((crohn* adj3 (disease* or enteritis*)) or colitis granulomat* or ileocolitis* or ileo colitis* or regional enteriti* or ((regional or terminal) adj3 ileiti*)).ti,ab,kf. (162035)
21 Diverticulitis/ (13556)
22 Diverticulitis, Colonic/ (8543)
23 diverticuliti*.ti,ab,kf. (19145)
24 or/13-23 (1201189)
25 12 and 24 (29805)
26 or/7,25 (262672)
27 Indocyanine Green/ (29582)
28 Fluorescein Angiography/ (56911)
29 indocyanin*.ti,ab,kf. (36638)
30 ((fluoresce* or green*) adj3 (angiograph* or intraluminal* or near infrared* or near infra red*)).ti,ab,kf. (53316)
31 (NIR adj3 fluoresce* imaging*).ti,ab,kf. (2538)
32 (green adj3 fluoresce*).ti,ab,kf. (106970)
33 ((intraoperat* or intra operat*) adj3 (angiograph* or fluoresce* or near infrared* or near infra red*)).ti,ab,kf. (7028)
34 (ICG or ICGA or ICGFA or ICGFI or ICGNIRF or ICYG or IGFA or NIR FI or NIRFI).ti,ab,kf. (26979)
35 (novadaq* or stryker* or (pinpoint* adj3 (fluoresce* or imag* or tower*)) or (spy* adj3 (elite* or angiograph* or fluoresce* or agent* or green* or imag* or portab* or handheld or tower*)) or SPY PHI* or SPYPHI* or SPY QP* or SPYQP*).ti,ab,kf. (4289)
36 ((rubina* or storz* or image1* or intuitive* or da vinci robot* or da vinci surg*) adj5 (fluoresce* or green* or near infrared* or near infra red* or NIR)).ti,ab,kf. (281)
37 (("1688" or "1788") adj3 (camera* or video* or 4k or spy* or imaging*)).ti,ab,kf. (16)
38 or/27-37 (228349)
39 26 and 38 (2180)
40 exp Animals/ not Humans/ (16442470)
41 39 not 40 (1901)
42 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6611036)
43 41 not 42 (1692)
44 limit 43 to english language [Limit not valid in CDSR; records were retained] (1614)
45 44 use cleed,coch (0)
46 economics/ (265290)
47 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1081177)
48 economics.fs. (470506)

49 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1327897)
50 exp "costs and cost analysis"/ (702581)
51 (cost or costs or costing or costly).ti. (341680)
52 cost effective*.ti,ab,kf. (469948)
53 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kf. (321031)
54 models, economic/ (16264)
55 markov chains/ or monte carlo method/ (110559)
56 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (70853)
57 (markov or markow or monte carlo).ti,ab,kf. (185447)
58 quality-adjusted life years/ (57727)
59 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (116988)
60 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (205455)
61 or/46-60 (3488810)
62 44 and 61 (56)
63 62 use medall,cctr (18)
64 45 or 63 (18)
65 exp colectomy/ (45871)
66 ileocolectomy/ (337)
67 (colectom* or hemicolectom* or sigmoidectom* or ileocolectom*).tw,kw,kf. (56605)
68 colorectal surgery/ (23861)
69 rectosigmoid resection/ (159)
70 colorectal anastomosis/ (2797)
71 rectum resection/ (10942)
72 (((bowel* or colon* or colorectal* or colosigmoid* or colo sigmoid* or coloanal* or colo anal* or colocolon* or ileocolon* or ileo colon* or mesocol* or meso col* or rectal* or rectum* or rectosigmoid* or recto sigmoid* or rectalsigmoid* or mesorectal* or meso rectal* or intersphincteric* or inter* sphincteric*) adj3 (surg* or operat* or procedure* or excision* or resection* or re section* or recision* or dissection* or anastomo* or reattach* or re attach* or reconnect* or re connect* or removal*)) or rectosigmoidectom*).tw,kw,kf. (200023)
73 (proctectom* or anterior resection*).tw,kw,kf. (21354)
74 or/65-73 (268559)
75 anastomosis leakage/ (27508)
76 anastomosis/ (53256)
77 ((anastomo* adj3 perfusion*) or ((anastomo* or perfusion* or blood flow* assess*) adj6 (leak* or integrit* or excision* or resection* or re section* or recision* or dissection* or reattach* or re attach or reconnect* or re connect* or removal*))).tw,kw,kf. (63700)
78 or/75-77 (117818)
79 exp colorectal tumor/ (716593)
80 ((bowel* or colon* or colorectal* or colosigmoid* or colo sigmoid* or coloanal* or colo anal* or colocolon* or ileocolon* or ileo colon* or mesocol* or meso col* or rectal* or rectum* or rectosigmoid* or recto sigmoid* or mesorectal* or meso rectal* or intersphincteric* or inter* sphincteric) adj3 (adenocarcinoma* or cancer* or carcinogen* or carcinoma* or malignan* or metasta* or neoplasm* or oncolog* or tumo?r*)).tw,kw,kf. (738146)
81 exp inflammatory bowel disease/ (302610)
82 (inflam* adj3 bowel disease*).tw,kw,kf. (185685)

83 ((bowel adj3 obstruct*) or (ulcerat* adj3 colitis*) or idiopath* proctocolitis* or colitis* gravis* or familial adenomatous polypos* or lynch syndrome*).tw,kw,kf. (200443)
84 ((crohn* adj3 (disease* or enteritis*)) or colitis granulomat* or ileocolitis* or ileo colitis* or regional enteriti* or ((regional or terminal) adj3 ileiti*)).tw,kw,kf. (162429)
85 diverticulitis/ (13556)
86 colon diverticulosis/ (6629)
87 diverticuliti*.tw,kw,kf. (19230)
88 or/79-87 (1313236)
89 78 and 88 (28374)
90 or/74,89 (274720)
91 indocyanine green/ (29582)
92 indocyanine green angiography/ (6440)
93 fluorescence angiography/ (57188)
94 indocyanin*.tw,kw,kf,dv. (36692)
95 ((fluoresce* or green*) adj3 (angiograph* or intraluminal* or near infrared* or near infra red*)).tw,kw,kf,dv. (54149)
96 (NIR adj3 fluoresce* imaging*).tw,kw,kf,dv. (2546)
97 (green adj3 fluoresce*).tw,kw,kf,dv. (106992)
98 ((intraoperat* or intra operat*) adj3 (angiograph* or fluoresce* or near infrared* or near infra red*)).tw,kw,kf,dv. (7402)
99 (ICG or ICGA or ICGFA or ICGFI or ICGNIRF or ICYG or IGFA or NIR FI or NIRFI).tw,kw,kf,dv. (27184)
100 (novadaq* or stryker* or (pinpoint* adj3 (fluoresce* or imag* or tower*)) or (spy* adj3 (elite* or angiograph* or fluoresce* or agent* or green* or imag* or portab* or handheld or tower*)) or SPY PHI* or SPYPHI* or SPY QP* or SPYQP*).tw,kw,kf,dv. (10757)
101 ((rubina* or storz* or image1* or intuitive* or da vinci robot* or da vinci surg*) adj5 (fluoresce* or green* or near infrared* or near infra red* or NIR)).tw,kw,kf,dv. (295)
102 (("1688" or "1788") adj3 (camera* or video* or 4k or spy* or imaging*)).tw,kw,kf,dv. (19)
103 or/91-102 (236772)
104 90 and 103 (2249)
105 (exp animal/ or nonhuman/) not exp human/ (12035863)
106 104 not 105 (2152)
107 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11566861)
108 106 not 107 (1281)
109 limit 108 to english language [Limit not valid in CDSR; records were retained] (1194)
110 Economics/ (265290)
111 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (151253)
112 Economic Aspect/ or exp Economic Evaluation/ (565430)
113 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1348309)
114 exp "Cost"/ (702581)
115 (cost or costs or costing or costly).ti. (341680)
116 cost effective*.tw,kw,kf. (478818)
117 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kw,kf. (330930)
118 Monte Carlo Method/ (85729)
119 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (74275)
120 (markov or markow or monte carlo).tw,kw,kf. (188919)

121 Quality-Adjusted Life Years/ (57727)
122 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (120344)
123 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (226300)
124 or/110-123 (2999691)
125 109 and 124 (46)
126 125 use emez (19)
127 64 or 126 (37)
128 127 use medall (12)
129 127 use cctr (6)
130 127 use coch (0)
131 127 use cleed (0)
132 127 use emez (19)
133 remove duplicates from 127 (27)

Grey Literature Search

Performed: February 7–9, 2024

Websites searched: Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), University Of Calgary Health Technology Assessment Unit, Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England (NHS), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Adelaide Health Technology Assessment, Australian Government Medical Services Advisory Committee, Monash Health Centre for Clinical Effectiveness, The Sax Institute, Australian Government Department of Health and Aged Care, Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S), Pharmac, Italian National Agency for Regional Health Services (Aegnas), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment (Austria), The Regional Health Technology Assessment Centre (HTA-centrum), Swedish Agency for Health Technology Assessment and Assessment of Social Services, Norwegian Institute of Public Health - Health Technology Assessments, The Danish Health Technology Council, Ministry of Health Malaysia - Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, Sick Kids PEDE Database, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used: indocyanine, green, fluorescence, angiography, infrared, ICG, ICGFI, novadaq, stryker, SPY, colectomy, colon resection, colorectal surgery, anastomotic, anastomoses, anastomosis, perfusion, angiographie, colectomie, anastomotique, anastomose

Clinical results (included in PRISMA): 1

Economic results (included in PRISMA): 1

Ongoing HTAs (PROSPERO/EUnetHTA/NICE/MSAC): 26

Ongoing clinical trials: 36

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool, version 1.0)

Author/trial name, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other biases
AVOID trial, 2024[49]	Low[h]	Unclear[i]	Unclear[j]	Low[e]	High[k]	Unclear[l]
De Nardi et al, 2020[34]	Low[b]	Low[c]	Unclear[g]	Low[e]	Low[f]	Low
EssentiAL trial, 2023[36]	Low[b]	Unclear[i]	Unclear[d]	Low[q]	Low[f]	Unclear[r]
FLAG trial, 2020[33]	Low[b]	Low[c]	Unclear[d]	Low[e]	Low[f]	Low
Gach et al, 2023[35]	Unclear[i]	Unclear[i]	Unclear[m]	Low[e]	Low[f]	High[n]
PILLAR III trial, 2021[32]	Unclear[i]	Unclear[i]	Unclear[d]	High[o]	Low[f]	High[p]

[a]Possible risk-of-bias levels: low, high, unclear.

[b]Computer-generated randomization.

[c]Randomization delivered via envelopes (whether opaque or sequentially numbered not specified) opened before start of surgery.

[d]Investigators and participants were not blinded; however, outcome measurement not likely to be influenced by lack of blinding.

[e]No missing outcome data.

[f]All prespecified outcomes in protocol or publication reported.

[g]Only study participants blinded to treatment allocation; however, outcome measurement not likely to be influenced by lack of blinding.

[h]Randomized in variable block sizes, stratified by site using online clinical trials database.

[i]Insufficient information.

[j]Group allocation not concealed from operating surgeon and was revealed to participants after the surgery. Authors note individuals analyzing the data may have been blinded up to a point.

[k]Some secondary outcomes deviate from the protocol (Meijer et al, 2022[55]). Specifically, AL-related mortality, surgical reintervention, and AL-related readmission are not reported as described but combined with other end points (i.e., all-cause mortality, reintervention, readmission). In addition, several subgroup analyses from the protocol are not reported, and no explanation is provided.

[l]Study performed in collaboration with Olympus Medical (The Netherlands) and funded by 3 industry parties who provided the indocyanine green dye and near-infrared imaging systems.

[m]Protocol states double-blind, but no information provided about outcome assessor or blinding.

[n]Insufficient information; publication is an interim analysis only with less than half the planned enrollment.

[o]347participants included in study, but analysis and results include data for only 343 and provide no explanation.

[p]Trial stopped early because of slow recruitment (347 enrolled) and was underpowered (planned sample size: 800, interim analysis planned once 450 enrolled). Further, the trial was sponsored by the manufacturer of the intervention technology.

[q]Outcomes of all randomized participants were analyzed.

[r]Trial sponsored by manufacturer of intervention technology; however, manufacturer had no role in study conduct, analysis, or publication.

Table A2: Risk of Bias[a] Among Comparative Cohort Studies (RoBANS)

Author, year	Selection of participants	Confounding variables	Measurement of intervention	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Brescia et al, 2018[37]	Low	Unclear[b]	Low	Low[c]	Low	Low[d]
Chen et al, 2023[38]	Low	Low	Low	Low[c]	Low	Low[d]
Flores-Rodriguez et al, 2023[39]	Low	Low[e]	Low	Low[c]	Low	Unclear[f]
Freund et al, 2021[40]	Low	Low[g]	Low	Low[c]	Low	Unclear[f]
Jafari et al, 2013[31]	Unclear[h]	High[i]	Unclear[j]	Low[c]	High[k]	High[l]
Marquardt et al, 2020[41]	Low	Low	Unclear[j]	Low[c]	High[m]	Low[d]
Neddermeyer et al, 2022[42]	Low	Unclear[n]	Low	Low[c]	Low	Low[d]
Starker and Chinn, 2018[43]	Low	Unclear[o]	Low	Low[c]	Low	Low[d]
Su et al, 2020[44]	Low	Unclear[b]	Unclear	Low[c]	Low[p]	Low[d]
Tsang et al, 2020[45]	Low	Unclear[b]	Low	Low[c]	Low[p]	Low[d]
Tueme-de la Peña et al, 2023[46]	Low	Unclear[b]	Unclear[j]	Low[c]	Low[p]	Low[d]
Watanabe et al, 2020[47]	Low	Low[q]	Unclear[j]	Low[c]	Low[p]	Unclear[r]
Watanabe et al, 2021[48]	Low	Low[q]	Unclear[j]	Low[c]	Low[p]	Low[d]

Abbreviation: RoBANS, Risk-of-Bias Assessment Tool for Nonrandomized Studies.

[a]Possible risk-of-bias levels: low, high, unclear.

[b]No matching; however, no statistically significant differences in participant characteristics between groups, including known prognostic factors.

[c]No blinding but unlikely to affect outcome measurement as outcomes are clearly defined and objective.

[d]All outcomes stated in methods or expected to be reported are reported.

[e]Propensity score analysis reported separately from main analysis.

[f]No protocol available and publication does not list all end points sought; however, expected outcomes for the field are reported.

[g]Groups matched on some key variables.

[h]Participants in both groups from same time period and centre; however, no clear eligibility criteria and use of intervention was at discretion of surgeon.

[i]No matching or consideration of confounders; several differences between groups in important variables for outcomes not adjusted for in analysis.

[j]No details on intervention measurement; was likely medical records or patient database given retrospective study design, but not reported.

[k]Authors state that 40 participants were included, but results available only for 38 (16 in intervention group, 22 in control group).

[l]Article states readmission analyzed, but no results reported.

[m]Authors state that 296 participants were included, but number undergoing low anterior resection (67 in intervention group, 59 control) and right hemicolectomy (76 in intervention group, 149 control) do not add up to that figure.

[n]No matching or adjustment between groups or in analysis. Main analysis was to test association of risk factors with anastomotic leak in univariate and multivariate regression.

[o]No matching; study compared participant characteristics, and some statistically significant differences present between intervention and control groups were not adjusted for in the analysis.

[p]Appears there are no missing data according to results tables.

[q]Protocol available, power calculation, propensity score matching of groups on important variables.

Notes for Table A2 continued

[r]Outome of oncologic clearance does not appear to be reported in results.

Table A3: GRADE Evidence Profile for the Comparison of Colorectal Resection, With ICGFI Versus Without

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Anastomotic leak							
6 (RCT)[32-36,49]	Serious limitations (−1)[a]	No serious limitations[b]	No serious limitations	Serious limitations (−1)[c]	Undetected[d]	None	⨁⨁ Low
13 (NRS)[31,37-48]	No serious limitations[e]	No serious limitations[b]	No serious limitations	No serious limitations[f]	Undetected[d]	None	⨁⨁ Low
Readmission							
1 (RCT)[49]	Serious limitations (−1)[a]	Not evaluable[g]	No serious limitations	Serious limitations (−1)[h]	Undetected	None	⨁⨁ Low
4 (NRS)[37,38,40,44,i]	No serious limitations	No serious limitations[b]	No serious limitations[j]	No serious limitations[k]	Undetected	None	⨁⨁ Low
Reoperation							
4 (RCT)[33-36]	No serious limitations[l]	Serious limitations (−1)	No serious limitations	Serious limitations (−1)[m]	Undetected	None	⨁⨁ Low
9 (NRS)[31,37,38,40,42,44,45,47,48]	No serious limitations[e]	No serious limitations[b]	No serious limitations[c]	No serious limitations[n]	Undetected	None	⨁⨁ Low
Sepsis							
1 (RCT)[34]	No serious limitations	Not evaluable[g]	No serious limitations	Very serious limitations (−2)[h]	Undetected	None	⨁⨁ Low
2 (NRS)[31,46]	Serious limitations (−1)[o]	No serious limitations	No serious limitations	Serious limitations (−1)[h]	Undetected	None	⨁ Very low
Length of stay							
5 (RCT)[33-36,49]	No serious limitations[l]	No serious limitations	No serious limitations	Serious limitations (−1)[h]	Undetected	None	⨁⨁⨁ Moderate
10 (NRS)[31,38,40,42,44-48]	No serious limitations[e]	No serious limitations	No serious limitations	No serious limitations[h]	Undetected	None	⨁⨁ Low
Mortality							
5 (RCT)[32-36,49]	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Very serious limitations (−2)[p]	Undetected	None	⨁ Very low
7 (NRS)[37,39,40,42,44,47,48]	No serious limitations[e]	No serious limitations	No serious limitations	Serious limitations (−1)[p]	Undetected	None	⨁ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICGFI, indocyanine green fluorescence imaging; NRS, nonrandomized study; RCT, randomized controlled trial.

[a]Full risk-of-bias assessment for RCTs is shown in Table A1.

[b]I^2 on meta-analysis was low; point estimates were reasonably consistent with overlap in confidence intervals.

[c]Confidence intervals of two-thirds of studies crossed no effect; optimal information size (OIS) was not met by most studies.

[d]Body of evidence comprised both larger and smaller studies with positive and null findings.

[e]Full risk-of-bias assessment for NRSs is shown in Table A2.

[f]Confidence intervals of 6 of 13 NRSs crossed null effect. OIS not met for most studies; however, effect size (relative and absolute) was clinically meaningful.

[g]Cannot assess given a single study.

Notes for Table A3 continued

[h]No confidence intervals available; did not meet OIS criterion.

[i]Two studies claim they assessed readmission but did not provide results by intervention group[34] or at all[31] and were therefore excluded from this assessment.

[j]One study was only of Crohn's disease patients undergoing a reoperation of an ileocolic resection,[40] which may not reflect the population of Ontario undergoing colorectal resections. However, this study contributed a smaller proportion of data for this outcome.[40]

[k]Direction of effect across studies was consistent, though individual estimates varied considerably (no confidence intervals available).

[l]One trial[35] that constituted a small proportion of the data was stopped early. Full risk-of-bias assessment for RCTs is shown in Table A1.

[m]Wide confidence intervals; OIS not met for any study.

[n]Confidence intervals of 5 of 8 studies crossed null effect and were wide. Direction of effect consistent across studies, but OIS not met.

[o]One study[31] was judged to be at high or unclear risk of bias in nearly all domains; however, it contributed only a small amount of data for this outcome, and the other study was mostly at low risk of bias. Full risk-of-bias assessment for NRSs is shown in Table A2.

[p]Zero or extremely few events; studies did not meet OIS criterion; no confidence intervals reported.

Appendix 3: Selected Excluded Studies – Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Jafari MD, Wexner SD, Martz JE, McLemore EC, Margolin DA, Sherwinter DA, Lee SW, Senagore AJ, Phelan MJ, Stamos MJ. Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study. J Am Coll Surg. 2015;220(1):82-92.	No comparator (control) group
Kim JC, Lee JL, Yoon YS, Alotaibi AM, Kim J. Utility of indocyanine-green fluorescent imaging during robot-assisted sphincter-saving surgery on rectal cancer patients. Int J Med Robot. 2016;12(4):710-17.	Noncontemporaneous controls
Losurdo P, Mis TC, Cosola D, Bonadio L, Giudici F, Casagranda B, Bortul M, de Manzini N. Anastomosis leak: Is there still a place for indocyanine green fluorescence imaging in colon-rectal surgery? A retrospective, propensity score-matched cohort study. Surg Innov. 2022;29(4):511-18.	Noncontemporaneous controls
Mizrahi I, Abu-Gazala M, Rickles AS, Fernandez LM, Petrucci A, Wolf J, Sands DR, Wexner SD. Indocyanine green fluorescence angiography during low anterior resection for low rectal cancer: Results of a comparative cohort study. Tech Coloproctol. 2018;22(7):535-40.	Noncontemporaenous controls
Picardi et al. Posted October 12, 2021. The use of indocyanine green fluorescence in the assessment of bowel perfusion in emergency and elective colorectal surgery. https://doi.org/10.21203/rs.3.rs-900541/v1.	Preprint only (unpublished)

Appendix 4: Selected Excluded Studies – Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Jayne D, Quirke P, Goh V, Hulme C, Kirby A, Corrigan N, Croft J, Brown J. INTACT: Intraoperative fluoresence angiography (IFA) to prevent anastomotic leak in rectal cancer surgery. Dis Colon Rectum. 2017 Jun 1;60(6):E344-44.	Wrong study design, did not assess cost-effectiveness
Kanabur P, Chai C, Taylor J. Use of indocyanine green for intraoperative ureteral identification in nonurologic surgery. JAMA Surg. 2020 Jun 1;155(6):520-1.	Wrong study design, did not assess cost-effectiveness
Pergamo MJ, Granieri MA, Weinberg A, Zhao L, Bernstein M, Grucela A. The use of ureteral stents with indocyanine green (ICG) in robotic colon surgery. Poster session presented at: SAGES Annual Meeting; 2017; Houston, TX.	Wrong study design, did not assess cost-effectiveness, not a full-text publication
Sandor Z, Ujfalusi Z, Varga A. Application of a self-developed, low-budget indocyanine green camera in surgical imaging – a single institution's experiences. J Fluoresc. 2023 Sep;33(5):2099-103.	Wrong study design, did not assess cost-effectiveness
Sherwinter D, Chandler P, Martz J. The use of tissue oxygen measurements compared to indocyanine green imaging for the assessment of intraoperative tissue viability of human bowel. Surg Endosc. 2022 Mar;36(3):2192-6.	Wrong study design, did not assess cost-effectiveness
Sosa MP, McNicholas DG, Bebla AB, Needham KA, Starker PM. All-cause 30- and 90-day inpatient readmission costs associated with 4 minimally invasive colon surgery approaches: a propensity-matched analysis using Medicare and commercial claims data. Surg Open Sci. 2022 Oct 1;10:158-64.	Wrong study design, did not assess cost-effectiveness
Vettoretto N, Foglia E, Ferrario L, Gerardi C, Molteni B, Nocco U, Lettieri E, Molfino S, Baiocchi GL, Elmore U, Rosati R. Could fluorescence-guided surgery be an efficient and sustainable option? A SICE (Italian Society of Endoscopic Surgery) health technology assessment summary. Surg Endosc. 2020 Jul;34(7):3270-84.	Abtract only[a]

[a]Full text available only in Italian.

Appendix 5: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A4: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of ICGFI Versus Visual Assessment Alone for the Visualization of Anastomotic Perfusion During Colorectal Surgery

Author, year, country	Is the study population appropriate for the review question?	Are the interventions appropriate for the review question?	Is the system in which the study was conducted sufficiently like the current Ontario context?	Is the perspective of the costs appropriate for the review question (e.g., Canadian public payer)?	Is the perspective of the outcomes appropriate for the review question?	Are all future costs and outcomes discounted appropriately (as per current CDA guidelines)?	Are QALYs derived using CDA's preferred methods, or is an appropriate social care–related equivalent used as an outcome? (If not, describe rationale and outcomes used in line with the analytical perspective taken)	Overall judgment[a]
Centre for Clinical Epidemiology and Evaluation, 2017, Canada[19]	Yes	Yes	Yes	Yes; public payer perspective	Yes	Yes; 3%	Yes	Directly applicable
Liu, 2022, Canada[61]	Yes	Yes	Yes	Partially; hospital payer perspective	Yes	Unclear; discount rate not reported	No	Partially applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

Abbreviations: CDA, Canada's Drug Agency; QALY, quality-adjusted life-year.

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A5: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of ICGFI Versus Visual Assessment Alone for the Visualization of Anastomotic Perfusion During Colorectal Surgery

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[b]
Centre for Clinical Epidemiology and Evaluation, 2017, Canada[19]	Yes	Yes	Yes	Partially; clinical inputs based on pooled OR of 4 comparative studies and 1 single-arm study (no RCTs)	Yes	Yes	Unclear[c]	Unclear[c]	Yes	Yes	No	Minor limitations
Liu, 2022, Canada[61]	Yes	Partially; time horizon not reported but appears to be short term	Partially; QALYs not included	Partially; cliical inputs based on meta-analysis of 20 comparative studies[64] (no RCTs)	Yes	Partially; did not include cost of physician remuneration (i.e., procedure cost) or costs of reoperation to treat AL and associated hospital stay	Yes	Yes	Partially; cost–consequence analysis; as such, incremental health effects not reported	Partially; PSA not conducted	No	Minor limitations

Abbreviations: AL, anastomotic leak; OR, odds ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; RCT, randomized controlled trial.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

[c]These values were redacted from the report.

Appendix 6: Additional Supporting Tables for the Primary Economic Evaluation

Table A6: CCI Intervention Codes for Procedures Involving Colorectal Surgery With Anastomosis

Code	Description	Type of anastomosis	Surgical approach
1.NM.87.DF	Excision partial, large intestine	Colocolostomy	Endoscopic
1.NM.87.RN	Excision partial, large intestine	Colocolostomy	Open
1.NM.87.DE	Excision partial, large intestine	Colorectal	Endoscopic
1.NM.87.RD	Excision partial, large intestine	Colorectal	Open
1.NM.87.DN	Excision partial, large intestine	Enterocolostomy	Endoscopic
1.NM.87.RE	Excision partial, large intestine	Enterocolostomy	Open
1.NM.89.DF	Excision total, large intestine	Ileorectal	Endoscopic
1.NM.89.RN	Excision total, large intestine	Ileorectal	Open
1.NM.91.DF	Excision radical, large intestine	Colocolostomy	Endoscopic
1.NM.91.RN	Excision radical, large intestine	Colocolostomy	Open
1.NM.91.DE	Excision radical, large intestine	Colorectal	Endoscopic
1.NM.91.RD	Excision radical, large intestine	Colorectal	Open
1.NM.91.DN	Excision radical, large intestine	Enterocolostomy	Endoscopic
1.NM.91.RE	Excision radical, large intestine	Enterocolostomy	Open
1.NQ.87.RD	Excision partial, rectum	Colorectal	Open abdominal
1.NQ.87.DE	Excision partial, rectum	Colorectal	Endoscopic
1.NQ.87.PB	Excision partial, rectum	Colorectal	Per orifice
1.NQ.89.SF	Excision total, rectum	Coloanal	Abdominal
1.NQ.89.KZ	Excision total, rectum	Coloanal	Abdominoperineal
1.NQ.89.GV	Excision total, rectum	Coloanal	Combined endoscopic with perineal
1.NQ.89.AG	Excision total, rectum	Coloanal	Combined endoscopic with per orifice

Abbreviation: CCI, Canadian Classification of Health Interventions.

Table A7: Annual Volumes of Colorectal Surgeries With Anastomosis in Ontario, 2021–2023

Year	Average volume
2021	7,478
2022	7,580
2023	7,624
Average annual volume	**7,561**

Abbreviation: DAD, Discharge Abstract Database

Source: DAD via IntelliHealth Ontario, 2012–2023.[90]

Table A8: Hospitalization Costs Associated With Reoperation for Major Anastomotic Leak in Ontario, 2019–2023

Fiscal year	Main diagnosis (ICD-10-CA code)	Principal treatments (CCI codes)	Average total cost
2022/23	Postoperative leak (T8183)	Excision partial, large intestine (1.NM.87) Excision total, large intestine (1.NM.89) Excision radical, large intestine (1.NM.91) Excision partial, rectum (1.NQ.87) Excision total, rectum (1.NQ.89)	$62,801
2021/22	Postoperative leak (T8183)	Excision partial, large intestine (1.NM.87) Excision total, large intestine (1.NM.89) Excision radical, large intestine (1.NM.91) Excision partial, rectum (1.NQ.87) Excision total, rectum (1.NQ.89)	$61,770
2020/21	Postoperative leak (T8183)	Excision partial, large intestine (1.NM.87) Excision total, large intestine (1.NM.89) Excision radical, large intestine (1.NM.91) Excision partial, rectum (1.NQ.87) Excision total, rectum (1.NQ.89)	$58,645
Annual average total cost			**$61,072**

Abbreviations: CCI, Canadian Classification of Health Interventions; DAD, Discharge Abstract Database; ICD-10-CA, International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada.
Source: DAD via IntelliHealth Ontario, 2012–2023.[90]

Table A9: Ratio of Average Physician Cost to Average Hospitalization Cost, Case Mix Group for Colostomy/Enterostomy in Ontario (All Age Groups), 2021–2022

Case mix group (description)	Estimated average hospital cost	Estimated average physician cost	Ratio
221 (colostomy/enterostomy)	$23,971	$5,158	0.22

Abbreviation: CIHI, Canadian Institute for Health Information.
Source: CIHI Patient Cost Estimator, 2022.[87]

Table A10: OHIP Schedule of Benefit Fee Codes for Relevant Procedures in Model

Procedure	Fee code	Description	Unit costs							Total cost, $
			Surgical assistant[a]			Surgeon	Anaesthesiologist[b]			
			Basic units	Time units	Cost, $	Cost, $	Basic units	Time units	Cost, $	
Reoperation[c] to address major AL	S167	Resection with anastomosis; large intestine, any portion	7	8	187.65	877.95	7	8	232.35	1,297.95
Stoma created during reoperation to address major AL	S157[d]	Creation of stoma (diverting or permanent)	–	–	–	400.05	–	–	–	400.05
Surgical procedure to reverse diverting stoma	S185	Removal of stoma (ostomy reversal)	6	8	175.14	504.70	7	8	232.35	912.19
Surgical procedure to address minor AL	Z594	Percutaneous drainage	–	–	–	331.90	–	–	–	331.90

Abbreviations: AL, anastomotic leak; OHIP, Ontario Health Insurance Plan.

[a]The amount payable to a surgical assistant is calculated by adding the number of basic and time units and multiplying that total by the unit fee. The surgical assistant unit fee is $12.51. Time units are calculated for each 15 minutes. The unit value of each 15-minute period is as follows: (1) during the first hour or less: 1 unit; (2) after the first hour: 2 units; and (3) after 2.5 hours: 3 units.

[b]The amount payable to the anaesthesiologist is calculated by adding the number of basic and time units and multiplying that total by the unit fee. The anesthesiologist unit fee is $15.49. Time units are calculated for each 15 minutes. The unit value of each 15-minute period is as follows: (1) during the first hour or less: 1 unit; (2) after the first hour up to and including the first 1.5 hours: 2 units; and (3) after 1.5 hours: 3 units.

[c]Calculations for reoperation to address a major anastomotic leak (with or without the creation of a stoma) are based on the assumption of an average total surgery time of 3 hours (based on guidance from clinical experts).

[d]This is an add-on code to S167 for patients requiring a stoma. When a stoma is created during the S167 operation, the surgeon claims 100% of billable fees for S167 and 85% of billable fees for S157 (see Surgical Preamble, OHIP Schedule of Benefits for Physician Services,[86] for further details).

Source: OHIP Schedule of Benefits for Physician Services.[86]

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About Us

We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

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