# Evidence report for ulcerative colitis refractory to medication therapy

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# Evidence report for ulcerative colitis refractory to medication therapy

## Part 1 - Scoping

Prepared by EBSCO Information Services

October 10, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

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# Abbreviations

## General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IQR – interquartile range
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SD – standard deviation
SE – standard error
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

## Abbreviations specific to this report that may appear in this report

IBD – inflammatory bowel disease
IPAA – ileal pouch anal anastomosis (sometimes also referred to as ileoanal pouch anastomosis)
PC – proctocolectomy
UC – Ulcerative colitis

**Note**: PC with IPAA is sometimes referred to as restorative proctocolectomy. We standardize on the term PC with IPAA throughout.

# Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Scoping was completed on October 10, 2019.

# Results – Criteria Selection for Critical Appraisal

## Population:

### *Inclusion criteria*

Adults with ulcerative colitis with unsatisfactory response to pharmacologic therapy (often referred to as "medication-refractory" ulcerative colitis, but perhaps better thought of as "near-medication-refractory" ulcerative colitis) eligible for proctocolectomy with IPAA

### *Exclusion criteria*

Patients with unequivocal indication for surgical intervention or for whom surgical intervention is not possible or appropriate (i.e., patients with absolute contraindications or strong relative contraindications)

### *Additional notes about the target population:*

The patient population in consideration is heterogeneous. For instance, patients considered to have medication-refractory or near-medication-refractory ulcerative colitis may not have tried the same medications, may not have the same extent or severity of inflammation, or may otherwise not be in the same overall point of the disease course. As was put simply by a recent German guideline[1] "Overall, the definition of therapy-refractory disease varies in the real clinical world". Accordingly, we consider it helpful to give a clinical gestalt of the target population for this evidence report and decision aid. Importantly, however, a patient for whom the clinician is considering proctocolectomy with IPAA need not fit the below-noted target description exactly for this evidence report and decision aid to be relevant. The target description is intended to help illustrate the "prototypical" patient in this situation to assist patients and clinicians who are navigating this difficult choice.

Target patients for this decision aid are patients who have not responded well to or are no longer responding well to standard treatment, including treatment escalation (e.g., trying systemic steroids for induction of remission and/or at least one biologic agent for induction and/or maintenance of remission). These patients will have also tried mesalamine or another 5-ASA agent unless they have an absolute contraindication to such or declined to try it. These patients are thus faced with the choice of either (1) further intensification/modification of pharmacologic treatment or (2) surgery.

These patients may also have an increased risk for near-future complications, such as toxic megacolon or perforation (frank or contained), or they may be in bad general health due to continued uncontrolled inflammatory disease process. They often have a high-risk profile with risk factors such as stenosis and/or extensive colitis with pronounced inflammation; they may also have been diagnosed with intraepithelial neoplasia within the last 5 years or have a first-grade relative who was diagnosed with colorectal cancer at an early age (<50 years of age).

This evidence report and decision aid considers proctocolectomy with ileal pouch anal anastomosis (PC with IPAA) for the option of surgery, though in certain cases PC with IPAA may be avoided in favor of a different

surgery (e.g., in patients who want to have children, given the possible association of reduced fertility with having PC with IPAA).

The decision to have PC with IPAA at some point in time throughout the course of disease is dependent on the various factors described above, and it might be hard for patients to find the right point in time to think about PC with IPAA and discuss it with their clinician. They may have already tried a range of medications and found them ineffective or insufficiently effective; alternatively, the medication(s) may have worked at one point, but seem not to work anymore. These patients may be experiencing inadequate symptom relief or even symptom worsening. One option in this situation is for patients to continue with medication(s) for as long as they consider their situation tolerable. This might mean accepting no improvement in symptoms, an increase in symptoms, complications of disease (such as perforation or stenosis), and/or a decreased quality of life. The alternative is to undergo PC with IPAA. However, PC with IPAA is a major surgery with many risks. This choice is one that is highly sensitive to preferences and individual disease perception, which are in turn influenced by the degree to which the following factors lead to distress or decrease in health-related quality of life: intensity of symptoms; extra-intestinal manifestation of disease; endoscopic evidence of the disease process (including structural changes such as stenosis); response to previous therapies; general adherence to medical therapies and willingness/desire to continue with such; and the patient's other comorbidities. Even as such, the decision is not necessarily easy. As noted by Kucharzik 2019,[1] one small retrospective survey of patients who had surgery[2] found that 53% of patients wished they had the surgery earlier than they did, with the remaining 47% feeling satisfied with when they had the surgery (none would have opted for a later surgery).

## Options:

### *Proctocolectomy with IPAA (+/- protective ileostomy)*

### *Continued pharmacologic therapy*

Note about options:
Comparative data are lacking for the option of proctocolectomy with IPAA (or proctocolectomy in general) versus continued pharmacologic management in patients with UC. This is reflected, for instance, in comprehensive guidelines on the management of UC.[1] Additionally, there is a general agreement about initial pharmacologic therapy in UC (e.g., 5-ASA agents are considered a cornerstone therapy), but if initial pharmacologic therapy proves insufficient, the medications tried thereafter can vary. Therefore, the option of continued pharmacologic therapy as used herein will, by definition, vary from patient to patient, because any given patient may have tried certain medications but not others. These considerations impact the FAQs to be answered as shown below.

## Outcomes:

Where outcomes will be answered with systematic searches, critical appraisal, and evidence synthesis, we will state the intended approach after we state the outcome(s) of interest for that FAQ (e.g., "The outcome of interest is all-cause mortality. We will obtain effect estimates from systematic reviews and meta-analyses of randomized, controlled trials or from individual trials if systematic reviews do not exist or meta-analysis is not the most appropriate method of synthesis."). Otherwise, where we say: "We will include a description of" (or something similar), we will answer the FAQ with descriptive responses, which do not involve systematic evidence searches, critical appraisal, or evidence synthesis.

### *FAQ 1: What does the treatment involve?*

For the option of proctocolectomy with IPAA, we will include a description of the treatment or procedure, including length of stay.

For the option of continued pharmacologic therapy, because of the number of potential medication regimens and because of the approach we will take for FAQ 2, we will state the patient will not have surgery, that s/he will work with his/her clinician to optimize his/her pharmacologic regimen, and that s/he may choose to have surgery later. We will also provide a list of possible medications that might be considered (e.g., different monoclonal antibodies), but given the number of possibilities, this list may not be exhaustive, and we will not describe dosing frequency for each possible option.

### *FAQ 2: What will my symptoms be?*

For the option of proctocolectomy with IPAA, treatment effectively eliminates the cause of the patient's symptoms from UC. We will note this qualitatively. However, proctocolectomy with IPAA still results in some symptoms that those with normal gastrointestinal anatomy and physiology would not experience (e.g., more frequent bowel movements). We will include a description of this, informed by guidelines on expected outcomes of proctocolectomy with IPAA.[1]

For the option of continued pharmacologic therapy, due to the heterogeneity of the patient population and this therapeutic option, we will answer this FAQ by stating that symptoms may get better, stay the same, or get worse, but that there may be other medications the patient can try before having surgery. We will also note that, although some patients may prefer to continue trying medication for as long as possible – even if their symptoms do not seem to be improving – continued medication therapy may only delay having surgery (rather than prevent it due to sufficient symptom control).[1]

### *FAQ 3: What will my quality of life be?*

For the option of proctocolectomy with IPAA, we will provide, as possible, estimates of quality of life after proctocolectomy with IPAA (e.g., pre-post studies), ideally from systematic reviews.

For the option of continued pharmacologic therapy, we will adopt a similar approach to that used for symptoms, but we will also incorporate the idea that quality of life will be impacted in a manner related to the patient's overall symptom burden and how this impacts his/her individual perception of his/her health/well-being, etc.

### *FAQ 4: What is my risk of developing colorectal cancer?*

For the option of proctocolectomy with IPAA, treatment effectively eliminates a person's risk of colorectal cancer, though there is a rare chance s/he may develop adenocarcinoma of the cuff/pouch.[3] We will include a description of this.

For the option of continued pharmacologic therapy, we will provide population-based estimates of colorectal cancer risk among patients with UC. Because of the heterogeneity of the population of interest, we will only seek to provide an overall estimate for the general population of people with UC, not patients with medication-refractory or near-medication-refractory UC who are on or who change to any specific pharmacologic regimen.

## *FAQ 5: Will I need to have colon cancer screenings?*

For the option of proctocolectomy with IPAA, the descriptive answer will simply be "No".

For the option of continued pharmacologic therapy, we will include a description of recommended screening intervals for patients with UC.

## *FAQ 6: What are the side effects or risks?*

For the option of proctocolectomy with IPAA, we will note there may be changes in bowel movements as specified in FAQ 2 ("What will my symptoms be?"). We will also seek estimates from systematic reviews for risks. Risks of interest include mortality, fecal incontinence, ileus, small bowel obstruction, anastomotic leak, infectious complications, fistula, pouchitis, and pouch failure/pouch loss/pouch excision. If possible, we will preferentially seek estimates for these specific risks over "overall complications" outcomes that combine minor and major complications or complications whose importance may otherwise differ substantially. If possible, we may differentiate these risks based on shorter-term (e.g., ≤30 days) and longer-term (e.g., >30 days) complications. Because the surgical procedure of interest can either include or not include protective/diverting ileostomy, we will not seek to differentiate risks quantitatively based on the presence/absence of protective/diverting ileostomy, but we will note qualitatively that anastomotic leaks and instances of pouch failure may be lower with protective/diverting ileostomy, but anastomotic strictures may be higher, and the choice of whether to have a protective/diverting ileostomy will be individualized for each patient.[4]

A risk that may be of particular interest for select patients is the possible risk of fertility problems associated with IPAA. This risk is noted in guidelines and systematic reviews,[1,5-7] albeit sometimes with uncertainty being expressed in the association/effect.[6] In line with guideline recommendations,[1] we will address this issue qualitatively, stating that patients interested in having children may wish to avoid IPAA and instead consider alternative surgical options or continued pharmacologic therapy.

For the option of continued pharmacologic therapy, we will sample guidelines and/or drug monograph data to provide a description of common side effects of various pharmacologic options the most common and serious risks of various pharmacologic options. We will also note that perioperative risk may be increased in people who have undergone prolonged medication therapy and that by continuing with medication therapy, they may be at risk for complications related to continued disease activity (e.g., perforation, stenosis, toxic megacolon).[1]

## *FAQ 7: When will I recover?*

For the option of proctocolectomy with IPAA, we will include a description of various recovery concepts as possible, including returning to work and sexual activity.

This FAQ does not apply for the option of continued pharmacologic therapy.

1 Kucharzik T, Dignass AU, Atreya R, Bokemeyer B, Esters P, Herrlinger K, Kannengießer K, Kienle P, Langhorst J, Lügering A, Schreiber S, Stallmach A, Stein J, Sturm A, Teich N, Siegmund B, Andus T, Autschbach F, Bachmann O, Baretton G, Baumgart DC, Bettenworth D, Bläker M, Buderus S, Büning J, Ehehalt R, Fellermann K, Fichtner-Feigl S, Götz M, Gross C, Hartmann F, Hartmann P, In der Smitten S, Häuser W, Helwig U, Kaltz B, Kanbach I, Keller KM, Klaus J, Koletzko S, Kroesen A, Kruis W, Kühbacher T, Leifeld L, Maaser C, Matthes H, Moog G, Ockenga J, Pace A, Reinshagen M, Rijcken E, Rogler G, Stange E, Veltkamp C, Zemke J. Updated S3-Guideline Ulcerative Colitis. German Society for Digestive and Metabolic Diseases (DGVS). Z Gastroenterol. 2019 Feb;57(2):162-241. doi: 10.1055/a-0824-0861. Epub 2019 Jan 17. PubMed
2 Neumann PA, Mennigen RB, Senninger N, Bruewer M, Rijcken E. Timing of restorative proctocolectomy in patients with medically refractory ulcerative colitis: the patient's point of view. Dis Colon Rectum. 2012 Jul;55(7):756-61. doi: 10.1097/DCR.0b013e318251e004. PubMed
3 Selvaggi F, Pellino G, Canonico S, Sciaudone G. Systematic review of cuff and pouch cancer in patients with ileal pelvic pouch for ulcerative colitis. Inflamm Bowel Dis. 2014 Jul;20(7):1296-308. doi: 10.1097/MIB.0000000000000026. PubMed
4 Weston-Petrides GK, Lovegrove RE, Tilney HS, Heriot AG, Nicholls RJ, Mortensen NJ, Fazio VW, Tekkis PP. Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy. Arch Surg. 2008 Apr;143(4):406-12. doi: 10.1001/archsurg.143.4.406. Review. PubMed
5 Waljee A, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. Gut. 2006 Nov;55(11):1575-80. Epub 2006 Jun 13. PubMed
6 Rajaratnam SG, Eglinton TW, Hider P, Fearnhead NS. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. Int J Colorectal Dis. 2011 Nov;26(11):1365-74. doi: 10.1007/s00384-011-1274-9. Epub 2011 Jul 16. PubMed
7 Lee S, Crowe M, Seow CH, Kotze PG, Kaplan GG, Metcalfe A, Ricciuto A, Benchimol EI, Kuenzig ME. The impact of surgical therapies for inflammatory bowel disease on female fertility. Cochrane Database Syst Rev. 2019 Jul 23;7:CD012711. doi: 10.1002/14651858.CD012711.pub2. PubMed

# Evidence report for ulcerative colitis refractory to medication therapy

## Part 4 - Evidence Synthesis

Prepared by EBSCO Information Services

October 17, 2019

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# Results – Summary of Findings

## *Notes about the target population:*

Formal inclusion/exclusion criteria for this evidence report can be found in Scoping. However, the patient population in consideration is heterogeneous. For instance, patients considered to have medication-refractory or near-medication-refractory ulcerative colitis may not have tried the same medications, may not have the same extent or severity of inflammation, or may otherwise not be in the same overall point of the disease course. As was put simply by a recent German guideline (Kucharzik 2019) "Overall, the definition of therapy-refractory disease varies in the real clinical world". Accordingly, we consider it helpful to give a clinical gestalt of the target population for this evidence report and decision aid. Importantly, however, a patient for whom the clinician is considering proctocolectomy with IPAA need not fit the below-noted target description exactly for this evidence report and decision aid to be relevant. The target description is intended to help illustrate the "prototypical" patient in this situation to assist patients and clinicians who are navigating this difficult choice.

Target patients for this decision aid are patients who have not responded well to or are no longer responding well to standard treatment, including treatment escalation (e.g., trying systemic steroids for induction of remission and/or at least one biologic agent for induction and/or maintenance of remission). These patients will have also tried mesalamine or another 5-ASA agent unless they have an absolute contraindication to such or declined to try it. These patients are thus faced with the choice of either (1) further intensification/modification of pharmacologic treatment or (2) surgery.

These patients may also have an increased risk for near-future complications, such as toxic megacolon or perforation (frank or contained), or they may be in bad general health due to continued uncontrolled inflammatory disease process. They often have a high-risk profile with risk factors such as stenosis and/or extensive colitis with pronounced inflammation; they may also have been diagnosed with intraepithelial neoplasia within the last 5 years or have a first-grade relative who was diagnosed with colorectal cancer at an early age (<50 years of age).

This evidence report and decision aid considers proctocolectomy with ileal pouch anal anastomosis (PC with IPAA) for the option of surgery, though in certain cases PC with IPAA may be avoided in favor of a different surgery (e.g., in patients who want to have children, given the possible association of reduced fertility with having PC with IPAA).

The decision to have PC with IPAA at some point in time throughout the course of disease is dependent on the various factors described above, and it might be hard for patients to find the right point in time to think about PC with IPAA and discuss it with their clinician. They may have already tried a range of medications and found them ineffective or insufficiently effective; alternatively, the medication(s) may have worked at one point, but seem not to work anymore. These patients may be experiencing inadequate symptom relief or even symptom worsening. One option in this situation is for patients to continue with medication(s) for as long as they consider their situation tolerable. This might mean accepting no improvement in symptoms, an increase in symptoms, complications of disease (such as perforation or stenosis), and/or a decreased quality of life. The alternative is to undergo PC with IPAA. However, PC with IPAA is a major surgery with many risks. This choice is one that is highly sensitive to preferences and individual disease perception, which are in turn influenced by the degree to which the following factors lead to distress or decrease in health-related quality of life: intensity of symptoms; extra-intestinal manifestation of disease; endoscopic evidence of the disease process (including structural changes such as stenosis); response to previous therapies; general adherence to medical therapies and willingness/desire to continue with such; and the patient's other comorbidities. Even as such, the decision is not necessarily easy. As noted by Kucharzik 2019, one small retrospective survey of patients who had surgery (Neumann 2012) found that 53% of patients wished they had the surgery earlier than they did, with the remaining 47% feeling satisfied with when they had the surgery (none would have opted for a later surgery).

## FAQ 1: What does the treatment involve?

### Proctocolectomy with ileal pouch anal anastomosis

People are asleep for the surgery. The colon and rectum will be removed. The end of the small intestine will be made into a pouch. The pouch will be attached to the anus. This allows people to have bowel movements using a toilet like they did before surgery. People may be in the hospital for 3 to 7 days. For a few months after the surgery, people may use a bag attached to their stomach to collect stool while the pouch heals. This will be removed when the pouch is ready to be used. People may be advised to change their diet, such as eating smaller meals more often and increasing the amount of water in their diet. People may also be advised to take vitamins.

### Continued pharmacologic therapy

You might try a different medication, try adding another medication, or try a different dose of the medication you already take. There are several medications that can be tried for refractory ulcerative colitis. These include medications like thiopurines, calcineurin inhibitors, or monoclonal antibody medications. You may have already tried some of them. Some people might try steroids, but these are usually used for the shortest amount of time possible. What people might try will depend on things like what they have tried already, other conditions they have, and the cost and side effects of the medicine.

(Sources consulted for these descriptive summaries include: Brewer 2019, Cleveland Clinic 2014, Crohn's and Colitis Foundation of America nd, DynaMed 2018, Kucharzik 2019, Mahmoud 2018, Mayo Clinic 2019, NIH 2018, Rubin 2019, UCSF Health nd)

## FAQ 2: What will my symptoms be?

### Proctocolectomy with ileal pouch anal anastomosis

After surgery, a patient's ulcerative colitis is usually considered cured, because the bad part of the intestines has been removed. Symptoms from ulcerative colitis – such as frequent bowel movements, suddenly feeling a strong need to have a bowel movement, bloody bowel movements, and stomach pain – will go away. However, some people may still get inflammation of their "pouch". This is discussed in "What are the side effects or risks?". Because of how the surgery changes the intestines, people may initially have bowel movements up to 15 times a day and they may be very soft or watery. Over time, people often have bowel movements less frequently and they are often more formed. However, many people still have 4 to 8 bowel movements a day. The consistency of the bowel movements may be like toothpaste. There are medications that help bulk the stool and decrease the number of bowel movements, but people do not have to take these.

### Continued pharmacologic therapy

Symptoms from ulcerative colitis – such as frequent bowel movements, suddenly feeling a strong need to have a bowel movement, bloody bowel movements, and stomach pain – may improve, stay the same, or get worse. This will depend on the patient and the medication that is tried. Examples of medications

that might be tried are listed in "What does the treatment involve?". Some people may prefer to keep trying medication for as long as possible even if their symptoms are not getting better. These people may hope they can avoid surgery. However, for some people, continuing with medication therapy may only delay surgery, not prevent it.

(Sources consulted for these descriptive summaries include: Brewer 2019, Cleveland Clinic 2014, Crohn's and Colitis Foundation of America nd, DynaMed 2018, Kucharzik 2019, Mahmoud 2018, Mayo Clinic 2019, NIH 2018, Rubin 2019, UCSF Health nd)

## FAQ 3: What will my quality of life be?

### Proctocolectomy with ileal pouch anal anastomosis

Overall, people usually have improvement in their quality of life after surgery. But it may take up to a year for the full benefits of the surgery to occur. (Moderate certainty evidence based on 2 systematic reviews without meta-analysis [Heikens 2012, Murphy 2015])

### Continued pharmacologic therapy

Your quality of life may improve, stay the same, or get worse. This will likely depend on if your symptoms improve, stay the same, or get worse.

(Sources considered/utilized not relevant for the above statement)

## FAQ 4: What is my risk of developing colorectal cancer?

### Proctocolectomy with ileal pouch anal anastomosis

People having this surgery cannot get cancer in the colon anymore, because the surgery removes the colon. Rarely, a person might get cancer in the pouch.

(Source consulted for this descriptive response: Selvaggi 2014)

### Continued pharmacologic therapy

Your risk of getting cancer in the colon or rectum depends on several things. This includes things like if you also have primary sclerosing cholangitis or a family history of cancer in the colon or rectum. Additionally, the risk of getting cancer in the colon or rectum may go up the longer you have had ulcerative colitis. (Low to Very low certainty evidence from 1 systematic review and meta-analysis [Castaño-Milla 2014])

Of 100 people who continue taking medication:

- if they have had ulcerative colitis for 10 years or less, 1 to 2 (1% to 2%) may get cancer in the colon or rectum in the next 10 years (Low certainty)

- if they have had ulcerative colitis for more than 10 years but less than 20 years, up to 4 (4%) may get cancer in the colon or rectum in the next 10 years (Very low certainty)
- if they have had ulcerative colitis for more than 20 years but less than 30 years, up to 5 (5%) may get cancer in the colon or rectum in the next 10 years (Very low certainty)

## FAQ 5: Will I need to have colon cancer screenings?

### Proctocolectomy with ileal pouch anal anastomosis

No

### Continued pharmacologic therapy

Yes. People with ulcerative colitis usually start having colonoscopies 6 to 8 years after they are first diagnosed. Depending on a person's risk factors, the colonoscopies may be done every 1 to 4 years. However, many people will likely get a colonoscopy every year.

(Sources consulted for these descriptive responses include: Kucharzik 2019, Rubin 2019)

## FAQ 6: What are the side effects or risks?

### Proctocolectomy with ileal pouch anal anastomosis

People may have changes in their bowel movements after this surgery (see "What will my symptoms be?").

A woman or man who has this surgery may have a harder time getting pregnant with his/her partner. People interested in having a child may want to consider a different surgery or continue to take medication to manage their symptoms.

After surgery, some people may have at least short-term problems with sex, but people may often find they are just as satisfied or more satisfied with their sex life.

Risks from having the surgery can be early (within 30 days of the surgery) or later (more than 30 days after the surgery).

Early risks (all evidence from 1 systematic review without meta-analysis [Peyrin-Biroulet 2016], all Very low certainty unless stated otherwise)
Of 100 people who have surgery:

- 10 to 45 (10% to 45%) may get an infection
    - In some cases, the infection may be serious. We do not have enough information to know how often this occurs.

- 14 to 30 (14% to 30%) may have their intestines stop moving. This often gets better within 3 days. Sometimes it lasts longer and may need more treatment to fix.
- 2 to 12 (2% to 12%) may have their intestines get blocked, which may need more surgery to fix
- <1 to 6 (<1% to 6%) may get a connection between two parts of the body that is not normal (often called a "fistula"). This could be a connection between different parts of the intestines, between the intestines and the bladder, between the intestines and the skin, or some other combination.
- <1 to 10 (<1% to 10%) may have leaking at the point where the surgeon joined their intestines together
- <1 to 3 (<1% to 3%) may die (Low certainty)

Later risks (all evidence from 1 systematic review without meta-analysis [Peyrin-Biroulet 2016], all Very low certainty unless stated otherwise)
Of 100 people who have surgery:

- 3 to 25 (3% to 25%) may have their intestines stop moving. This often gets better within 3 days. Sometimes it lasts longer and may need more treatment to fix.
- 17 (17%) may have their intestines get blocked, which may need more surgery to fix (Moderate certainty)
- 8 to 41 (8% to 41%) may have infection or inflammation of their pouch, which is often treated with antibiotics
- <1 to 17 (<1% to 17%) may have their pouch not work or need to have their pouch removed
- <1 to 8 (<1% to 8%) may get a connection between two parts of the body that is not normal (often called a "fistula")
- 21 to 22 (21% to 22%) may have times when they cannot control when they have a bowel movement (Low certainty)

If the surgeon also does something called a "protective ileostomy" or "diverting ileostomy", this may:

- lower the risk of leaking at the point where the intestines are joined together
- lower the risk of the pouch not working
- increase the risk of part of the intestines becoming too small

(In addition to the 1 systematic review without meta-analysis used for "early" and "late" risks [Peyrin-Biroulet 2016], the following sources were consulted for descriptive responses included in this FAQ: Cornish 2007, Crohn's and Colitis Foundation of America nd, Kucharzik 2019, Lee 2019, Rajaratnam 2011, UCSF Health nd, Vather 2013, Waljee 2006, Weston-Petrides 2008)

## Continued pharmacologic therapy

Side effects and risks from medication depend on the specific medication that might be tried.

Side effects from medication may include:

- nausea, vomiting, or stomach pain
- cough, shortness of breath, upper respiratory infection, or pain in the chest
- fatigue, headache, or dizziness
- numbness, pain, tingling, or strange feelings in different parts of the body
- joint pain

- increased appetite and weight gain
- mood changes
- injection site pain (if the medicine is injected)

Although serious risks from medication may be uncommon, risks might include:

- infection and decreased ability to fight infection
- decreased ability to make important parts of blood (red blood cells, white blood cells, and/or platelets)
- heart failure or bad heart rhythms
- passing out
- pancreatitis or hepatitis
- severe allergic reaction
- severe rash, which can be life-threatening in its worst form
- certain cancers, such as lymphoma
- serious problems in the brain from increased blood pressure or a virus, which may or may not be reversible and can cause death

People who continue to take medicine still have the bad part of the intestines inside them. Because of this, there is a risk the intestines could:

- get too small in certain areas
- get a tear in them, which is an emergency
- get dangerously large in certain areas, which is an emergency

Although patients who continue to take medicine can decide to have surgery later, they may have more risks from surgery than people who have surgery earlier.

Patients can discuss possible side effects and risks in more detail with their clinician.

(Sources consulted for this descriptive response include: DynaMed 2018, Kucharzik 2019, Rubin 2019)

## FAQ 7: When will I recover?

### Proctocolectomy with ileal pouch anal anastomosis

For about 6 to 8 weeks after surgery, people may be advised to avoid certain foods. Most people can return to the things they normally do in about 4 to 8 weeks, including work and sex. Each person should talk with the surgeon about when it is okay to return to certain activities.

### Continued pharmacologic therapy

Does not apply

(Sources consulted for these descriptive summaries include: Brewer 2019, Cleveland Clinic 2014, Crohn's and Colitis Foundation of America nd, DynaMed 2018, Kucharzik 2019, Mahmoud 2018, Mayo Clinic 2019, NIH 2018, Rubin 2019, UCSF Health nd)

# Abbreviations

## General abbreviations that may appear in this report

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IPAA – ileal pouch anal anastomosis (sometimes also referred to as ileoanal pouch anastomosis)
PC – proctocolectomy
UC – Ulcerative colitis

**Note**: PC with IPAA is sometimes referred to as restorative proctocolectomy. We standardize on the term PC with IPAA throughout.

# Methods

Where evidence is very limited, or the FAQ is scoped as a descriptive response, such that no evidence synthesis or processing is applied, the descriptive summary/-ies will be given.

For each FAQ for which evidence synthesis or processing is considered, the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. For each outcome, Evidence Synthesis Process tables will then articulate the method selected for evidence synthesis and justification of that method. We will do this for the effect estimate (i.e., answering the question "Is there a difference between the intervention and comparator?") and results will be presented with GRADE-based certainty of evidence ratings related to the certainty of effect estimates. For FAQs which require noncomparative/option-specific responses (i.e., the FAQ is "What will happen with this option?" rather than "How do things change with this option?") the Evidence Synthesis Process tables will be extended to include the method to produce noncomparative responses.

**For summary statements representing a plain language summary of evidence appraisal and synthesis**

We will include the following 2 items immediately after the summary statement as a parenthetical, regardless of whether they occur in the Summary of Findings section or the individual FAQs in the body of the Evidence Synthesis document:

- our certainty in the summary statement (categorized as High, Moderate, Low, or Very low), and
- the number and type of studies informing the statement, as well as a label for the studies in "[Author] [Year]" format.

If the study informing the summary statement is a systematic review and meta-analysis, then unless there are compelling reasons to proceed in a different manner, we will cite the systematic review and meta-analysis as the source. We will do this even if the result on which our summary statement is based comes from a subset of studies in that systematic review and meta-analysis (e.g., a meta-analysis of 5 out of 10 studies, because only 5 of the 10 reported on the outcome of interest). If EBSCO Information Services conducts its own meta-analysis of studies to inform a summary statement, we will list the individual studies.

**For summary statements representing a plain language summary of descriptive sources**

Certainty rating and provision of details about contributing studies do not apply. Accordingly, we will not include a parenthetical at the end of the summary statement. However, when descriptive summaries appear in the Summary of Findings section, we will include a general parenthetical citation of the references we consulted. We will place this at the end of the relevant FAQ in the Summary of Findings section. For summary statements occurring in the body of the Evidence Synthesis document, we will provide this general parenthetical citation as part of the longer descriptive summary component that precedes the simplified summary statement.

## Search Summary

**Number of articles screened and selected**

| | Screened | Selected* |
|---|---|---|
| **1st-round (DynaMed)** | 23 | 1 |
| **2nd-round (Systematic review searches)** | 59 | 5 |
| **3rd-round (Study tracing)** | Not applicable | |
| **4th-round (Original article searches)** | Not applicable | |
| ***Total*** | *82* | *6* |

* Number shown is after deduplication

| | Articles selected for evaluation (Author Year) |
|---|---|
| **Systematic reviews** | 6 (Castaño-Milla 2014, Heikens 2012, Lutgens 2013, Murphy 2015, Peyrin-Biroulet 2016, Wheat 2016)* |
| **Randomized, controlled trials** | 0 |
| **Other article types** | 0 |

*Lutgens 2013 and Wheat 2016 were not advanced to Part 4 Evidence Synthesis for reasons stated in Part 3

# Results – Synthesis Details

## FAQ 1: What does the treatment involve?

### Proctocolectomy with ileal pouch anal anastomosis

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

Patients are asleep for the surgery, and the hospital stay after surgery may be about 3 to 7 days. During the surgery, the colon and rectum are removed, and the end part of the small intestine, called the ileum, is turned into a pouch (this is the "ileal pouch" part of "ileal pouch anal anastomosis"). The pouch is commonly in the shape of the letter "J". For this reason, the ileal pouch is sometimes called a "J pouch". However, other pouch types exist (e.g., a pouch in the shape of an "S" or "W"). Once the pouch is formed, the surgeon attaches it to the anal canal (this is the "anal anastomosis" part of "ileal pouch anal anastomosis"). This helps a person maintain control over his/her bowel movements. However, the areas involved in the surgery often need time to heal before they are fully functional. For instance, the pouch and the muscles in the anal canal and anus may need to gain or regain strength after surgery, so a person may notice frequent bowel movements initially, perhaps up to 15 a day. The stool is also often much softer and may even be liquid-like in the early postsurgical period. Over time, bowel movements generally become more formed and less frequent, though people often still have between 4 and 8 bowel movements a day, and the stool may still be softer than it was prior to surgery (perhaps like the consistency of toothpaste). Depending on the nature of a person's UC, s/he may have bowel movements frequently even before surgery, and the stool may also be soft due to the inflammatory process decreasing transit time and the absorptive capacity of the colon. This somewhat mirrors the reason why bowel movements may change in frequency and texture after surgical removal of the colon and rectum: the intestines are much shorter without the colon and rectum (thus decreasing transit time), and the colon is also responsible for absorbing a lot of fluid from fecal effluent. If desired, bulking and/or antimotility medications can be used to help bulk the stool and/or decrease the number of bowel movements a person has. Because of how the gastrointestinal tract is changed, people may be advised to alter their diet, such as eating smaller and more frequent meals (to prevent large food boluses) and increased water intake (to prevent dehydration, given the loss of the absorptive capacity of the colon). Some may also be advised to take vitamin and/or mineral supplements.

Some patients may also receive a temporary ileostomy, which is often called a "diverting ileostomy" or "protective ileostomy". When this is done, the ileostomy connects a part of the ileum above the IPAA to an opening in the abdominal wall. The opening in the abdominal wall is covered by a bag (called an "ostomy bag"). The ileostomy directs fecal matter into the ostomy bag while the IPAA heals (no fecal matter will go beyond the ileostomy, because the IPAA is surgically separated from the rest of the small intestine during the temporary ileostomy phase). Once the IPAA has had a chance to heal (often after 8 to 16 weeks), the ileostomy will be reversed. This means there will be no opening in the abdomen, no ostomy bag, and the person will start using the IPAA to have bowel movements.

(Brewer 2019, Cleveland Clinic 2014, Crohn's and Colitis Foundation of America nd, Mahmoud 2018, Mayo Clinic 2019, NIH 2018, UCSF Health nd)

### *Descriptive Summary Results for FAQ 1*

**People are asleep for the surgery. The colon and rectum will be removed. The end of the small intestine will be made into a pouch. The pouch will be attached to the anus. This allows people to have bowel movements using a toilet like they did before surgery. People may be in the hospital for 3 to 7 days. For a few months after the surgery, people may use a bag attached to their stomach to collect stool while the pouch heals. This will be removed when the pouch is ready to be used. People may be advised to change their diet, such as eating smaller meals more often and increasing the amount of water in their diet. People may also be advised to take vitamins.**

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## Continued pharmacologic therapy

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

Given this evidence report concerns patients with refractory UC, we assume all patients are either already taking or have already tried 5-aminosalicylic acid agents (e.g., mesalamine). As stated earlier, target patients for this decision aid are patients who have not responded well to or are no longer responding well to standard treatment, including treatment escalation (e.g., trying systemic steroids for induction of remission and/or at least one biologic agent for induction and/or maintenance of remission). These patients will have also tried mesalamine or another 5-ASA agent unless they have an absolute contraindication to such or declined to try it. Therefore, for these patients, continued pharmacologic therapy means further intensification and/or modification of pharmacologic treatment

Medications that might be considered for refractory UC include, but are not limited to:

- purine analogs (sometimes called “thiopurines”): azathioprine and its metabolite 6-mercaptopurine
- calcineurin inhibitors: cyclosporine, tacrolimus
- biologics:
    - anti-TNF agents (infliximab, adalimumab, golimumab)
    - anti-integrin agent (vedolizumab)
- systemic corticosteroids (for inducing remission, but ideally not for maintenance, though there are cases of “steroid-dependent” UC)

(DynaMed 2018, Kucharzik 2019, Rubin 2019)

***Descriptive Summary Results for FAQ 1***

**You might try a different medication, try adding another medication, or try a different dose of the medication you already take. There are several medications that can be tried for refractory ulcerative colitis. These include medications like thiopurines, calcineurin inhibitors, or monoclonal antibody medications. You may have already tried some of them. Some people might try steroids, but these are usually used for the shortest amount of time possible. What people might try will depend on things like what they have tried already, other conditions they have, and the cost and side effects of the medicine.**

## FAQ 2: What will my symptoms be?

### Proctocolectomy with ileal pouch anal anastomosis

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

In Part 1 Scoping, we specified we would note that PC with IPAA functionally cures the patient's UC, because the colon is removed. We also stated we would include a description of how this surgery might impact a person's bowel movements as a part of answering this FAQ. We have included the information pertaining to bowel movements within "FAQ 1: What does the treatment involve?", but we have placed the bolded synthesis statement in this FAQ for consistency and because frequency and nature of bowel movements more directly matches this FAQ.

***Descriptive Summary Results for FAQ 2***

**After surgery, a patient's ulcerative colitis is usually considered cured, because the bad part of the intestines has been removed. Symptoms from ulcerative colitis – such as frequent bowel movements, suddenly feeling a strong need to have a bowel movement, bloody bowel movements, and stomach pain – will go away. However, some people may still get inflammation of their "pouch". This is discussed in "What are the side effects or risks?". Because of how the surgery changes the intestines, people may initially have bowel movements up to 15 times a day and they may be very soft or watery. Over time, people often have bowel movements less frequently and they are often more formed. However, many people still have 4 to 8 bowel movements a day. The consistency of the bowel movements may be like toothpaste. There are medications that help bulk the stool and decrease the number of bowel movements, but people do not have to take these.**

### Continued pharmacologic therapy

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

In Part 1 Scoping, we specified we would note that, due to the heterogeneity of the patient population and this therapeutic option, we will answer this FAQ by stating that symptoms may get better, stay the same, or get worse, but that there may be other medications the patient can try before having surgery. We also stated that we would specify that medication may only delay (rather than prevent) surgery.

***Descriptive Summary Results for FAQ 2***

**Symptoms from ulcerative colitis – such as frequent bowel movements, suddenly feeling a strong need to have a bowel movement, bloody bowel movements, and stomach pain – may improve, stay the same, or get worse. This will depend on the patient and the medication that is tried. Examples of medications that might be tried are listed in "What does the treatment involve?". Some people may prefer to keep trying medication for as long as possible even if their symptoms are not getting better. These people may hope they can avoid surgery. However, for some people, continuing with medication therapy may only delay surgery, not prevent it.**

## FAQ 3: What will my quality of life be?

### Proctocolectomy with ileal pouch anal anastomosis

Evidence concerning quality of life comes from two systematic reviews without meta-analysis: Heikens 2012 (33 studies totaling 4,790 people) and Murphy 2015 (13 studies totaling 783 people). The systematic reviews had different goals (leading to the different number of included studies and patients): Heikens 2012 sought to assess quality of life in patients having PC with IPAA, whereas Murphy 2015 sought to compare quality of life in patients receiving PC with IPAA versus patients receiving PC with ileostomy. Because our evidence report is only concerned with PC with IPAA, we only extracted the data for PC with IPAA from Murphy 2015. Due to the varied ways in which outcomes were assessed and reported, evidence review tables below present these results in a simplified form while still capturing each of the studies included in these systematic reviews. Neither performed any meta-analysis, so pooled results are not available.

As part of completing this evidence report, we also consulted the recent German guideline (Kucharzik 2019). This yielded 4 additional citations of potential interest: Fazio 1995, Heuschen 1998, Lichtenstein 2006, and van der Valk 2015. However, Lichtenstein 2006 is a narrative review (systematic literature review methods were not specified) and includes only a portion of the studies captured by Heikens 2012, and Heuschen 1998 is already included in Heikens 2012. Fazio 1995 was likely not included in Heikens 2012 due to the follow-up requirements for inclusion in Heikens 2012 (minimum of 12 months, versus range of 1 to 125 months in Fazio 1995). Additionally, Fazio 1995 only had complete data for function/quality of life for 645/1,005 (64%) of patients, but results were still consistent with those seen in Heikens 2012 (the complications data from Fazio 1995 are captured by the Peyrin-Biroulet 2016 systematic review that we address in FAQ 6). Finally, van der Valk 2015 is a case-control study with 115 patients of relevance for this evidence report. Although it found no clear difference in Inflammatory Bowel Disease Questionnaire scores between those who underwent PC with IPAA (n = 81) versus those who were on anti-TNF medications (n = 34), it also found quality-adjusted life years (using the EuroQOL 5-dimension scale) may favor PC with IPAA to a certain degree. However, we question whether these case-control data should be given prominent consideration in light of the data available in the systematic review by Heikens 2012. Therefore, these 4 sources were deemed not to add meaningfully to what is provided by Heikens 2012 and Murphy 2015.

#### *Evidence Review Tables for FAQ 3*

**Study details and postsurgical results for health-related quality of life and/or health status for included studies (Heikens 2012)**

| Study | Follow-up (months) | No. people | Did all have UC? | Quality rating (per Heikens 2012) | Outcome measured (after surgery unless stated otherwise) | Conclusion |
|---|---|---|---|---|---|---|
| McLeod et al | 12 | 37 | Yes | High | HRQoL | usually improves |
| Polle et al | 12 | 53 | No (19 did not have UC)* | High | HS and HRQoL (before and after) | both improve |

| | | | | | | |
|---|---|---|---|---|---|---|
| Thirlby et al | 12 | 27 | Yes | High | HS (before and after) | improves and is similar to the general population |
| Delaney et al | 55 | 1285 | Yes | Moderate | HRQoL | careful selection permits "acceptable" outcome |
| Hahnloser et al | 130 | 1885 | Yes | Moderate | HS (before and after) | "is preserved" |
| Heuschen et al | 43 | 243 | No (58 did not have UC)* | Moderate | HS | similar to the general population if there are no postoperative complications |
| Scarpa et al | 101 | 36 | Yes | Moderate | HS | medications, frequency of bowel movements, presence/absence of pouchitis, age at diagnosis, and postoperative complications all influence |
| Berndtsson and Oresland | 12 | 32 | Yes | Moderate | HS and HRQoL (before and after) | no change |
| Carmon et al | 51 | 78 | Yes | Moderate | HS | similar to the general population |
| Muir et al | 12 | 20 | Yes | Moderate | HS (before and after) | improves |
| Robb et al | 45 | 138 | Yes | Moderate | HS | "increases … significantly" and is similar to the general population |
| Young et al | 68 | 48 | Yes | Moderate | HRQoL (before and after) | poor in most |
| Camilleri-Brennan | 41 | 19 | Yes | Moderate | HS | high |
| Holubar and Hyman | 85 | 51 | Yes | Moderate | HS | "extremely well preserved" |
| Martin et al | 46 | 29 | Yes | Moderate | HS | similar to those "in remission or with mild symptoms" |
| Mowschenson et al | 75 | 111 | No (3 did not have UC) | Moderate | HS | normal in most |
| Pace et al | 24 | 13 | Yes | Moderate | HS | "generally satisfying" |
| Weinryb et al | 82 | 40 | Yes | Moderate | HS | good |
| Coffey et al | 67 | 54 | Yes | Moderate | HRQoL | dietary choices and timing, preoperative diagnosis, and pregnancy all influence |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hauser et al | 80 | 61 | Yes | Moderate | HS | "also determined by anxiety and extra-intestinal manifestations" |
| O'Bichere et al | 13 | 30 | Yes | Moderate | HS | "improved pelvic function" leads to improvement |
| Richards et al | 48 | 56 | Yes | Moderate | HS and HRQoL | similar to the general population |
| Sagar et al | 12 | 103 | Yes | Moderate | HS | good |
| Seidel et al | 31 | 55 | No (20 did not have UC)* | Moderate | HS | good, with most having an improvement |
| Steens et al | 67 | 36 | No (5 did not have UC) | Moderate | HS and HRQoL | "only slightly decreased" |
| Willis et al | 96 | 24 | Yes | Moderate | HS | "significantly better" if no major postoperative issues |
| Barton et al | 33 | 37 | Yes | Low | HS | good |
| Pezim and Nicholls | 28 | 51 | No (7 did not have UC) | Low | HS | satisfactory |
| Tiainen and Matikainen | 96 | 68 | Yes | Low | HS | similar to the general population |
| Lecointe-Besancon et al | 31 | 13 | Yes | Low | HRQoL | "similar between continent and incontinent patients" |
| Brunel et al | 35 | 27 | Yes | Low | HRQoL (before and after) | improved |
| Hildebrandt et al | NR | 5 | Yes | Low | HRQoL | 9/10 |
| Vendrell et al | NR | 25 | Yes | Low | HS | improved |

HRQoL, health-related quality of life; HS, health status (considered a subset of HRQoL); NR, not reported; UC, ulcerative colitis

* These 3 studies (of the 33 studies included in Heikens 2012) had <80% of the intended population. Importantly, however, their results are not substantively different from the overall inference one can draw from the other studies or from Heikens 2012 as a whole (i.e., that quality of life/health-related quality of life appears to be good after proctocolectomy with ileal pouch anal anastomosis). One might consider a certainty downgrade for indirectness if there were an important population mismatch, but we do not think there is justification for this downgrade here when the results are consistent regardless of whether one were to include or exclude these 3 studies.

Of the above 33 studies, 27 had results that permitted classification via a trichotomy of "good outcome", "bad outcome", or "no difference" (6 were classified as "other" due to not clearly describing a benefit, harm, or no difference). Examples of how the results were classified are:

- good outcome – "improved", "9/10", "is similar to the general population"
- bad outcome – "poor in most", "only slightly decreased"
- no difference – "extremely well preserved", "no change"
- other – saying that things like medications and age at diagnosis influence the outcome, but giving no indication of how the outcome itself fared; saying that "improved pelvic function" leads to improvement, but giving no indication of whether most patients experienced what the authors categorized as "improved pelvic function"; saying that quality of life was similar between continent and incontinent patients, but giving no indication of how quality of life compared to presurgical levels.

Not all studies assessed quality of life or health status before and after surgery. However, studies that only assessed outcomes after surgery often included some method that permitted inference – even if somewhat indirectly – into how the surgery impacted people. For example, Robb et al. compared patient-reported health status among people who underwent surgery with health status for the general population, and they noted the results to be comparable (i.e., health status for the surgical group was "similar to the general population"). This implies an improvement, because the health status of those who received surgery was similar to the health status of the general population, and this is unlikely to be true for patients with medication-refractory UC or near-medication-refractory UC. More generically, a study assessing health status or quality of life only after the surgery took place could also simply use a questionnaire that asked those people if they felt their quality of life or health status has stayed the same, increased, or decreased since having the surgery. So, even studies without an explicit measurement pre- and post-surgery can still offer insight. We also note the overall pattern of results is consistent regardless of whether one restricts to studies that explicitly measured pre- and post-surgery.

Additionally, as noted in the footnote for the above table, there were 3 studies (of the 33 studies included) that had <80% of the intended population. Importantly, however, their results are not substantively different from the overall inference one can draw from the other studies or from Heikens 2012 as a whole (i.e., that quality of life/health-related quality of life appears to be good after proctocolectomy with ileal pouch anal anastomosis). One might consider a certainty downgrade for indirectness if there were an important population mismatch, but we do not think there is justification for this downgrade here when the results are consistent regardless of whether one were to include or exclude these 3 studies.

If considering the studies that were classifiable via the aforementioned trichotomy, 22/27 studies (81.5%) suggested a good outcome, 2/27 studies suggested a bad outcome (7.4%), and 3/27 studies (11.1%) suggested findings of no difference. Additionally, all 3 studies considered high quality (2 of which assessed findings before and after surgery) suggested a good outcome.

The above findings summarily support a Moderate certainty conclusion that most have an improvement in health status or health-related quality of life after PC with IPAA, with a downgrade for imprecision (results not reported in sufficient detail to permit assessment of precision). Although only a few studies were rated as high quality, the results from these studies were consistent with the general finding of improvement in health status or health-related quality of life after PC with IPAA.

**Study details and postsurgical results for various quality of life measures in included studies (Murphy 2015)**

| Study | No. people | Follow-up in months (mean unless otherwise specified) | Outcome | Results (% or mean value, unless stated otherwise) |
|---|---|---|---|---|
| Emblem et al | 19 | 48 | Social restriction | 0% |
| Pemberton et al | 298 | 47 (median) | Overall satisfaction | 95% |
| | | | Return to work/school | 98% |
| McLeod et al | 37 | NR | TTOT (0–1, higher scores better) | 0.95 |
| | | | DQO (0–1, higher scores better) | 0.87 |
| | | | SIP (0–100, lower scores better) | 1.2 |
| Liddell et al | 25 | 40 | Lifestyle satisfaction (1–7, higher scores signal more improvement) | 5.48 |
| Kartheuser et al | 29 | 41 | Well-being | 91% |
| | | | No social restriction | 86% |
| | | | No work restriction | 91% |
| | | | Overall satisfaction | 91% |
| Jimmo et al | 55 | 12 | IBDQ (32–224, higher scores better) | 205 |
| O'Bichere et al | 30 | 13 | SF-36 (0–100, higher scores better) | 78 |
| Seidel et al | 55 | 31 (combined for IPAA and ileostomy groups) | Overall QOL better since operation (always) | 87% |
| Nordin et al | 56 | NR | SF-36, social functioning (0–100, higher scores better) | 70.2 |
| | | | IBDQ, bowel symptoms subscale (10-70, higher scores better) | 54.4 |
| | | | IBDQ, emotional function subscale (12-84, higher scores better) | 64.8 |
| Camilleri-Brennan et al | 19 | 41 (median) | SF-36 (0–100, higher scores better) | 85.9 |
| | | | IBDQ (transformed to a 0-100 scale, higher scores better) | 85.4 (median) |
| Wang et al* | 48 | 41 | SF-36, physical scale (0–100, higher scores better) | 55.5 |
| | | | SF-36, mental scale (0–100, higher scores better) | 55 |
| | | | IBDQ (32–224, higher scores better) | 181.1 |
| van der Valk et al | 77 | NR | EQ-5D index (0–1, higher scores better) | 0.85 |
| Kuruvilla et al | 35 | 157 | EQ-5D index (0–1, higher scores better) | 0.85 |

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| | | | | |
|---|---|---|---|---|
| | | | EQ VAS (0–100, higher scores better) | 85.4 |
| | | | SIBDQ (10–70; higher scores better) | 62.2 |
| | | | FIQL (1–4, higher scores better) | 3.7 |
| | | | SQOL, sexuality/body (0-100, higher scores better) | 93.1 |
| | | | SQOL, work/social function (0-100, higher scores better) | 93.4 |
| | | | SQOL, financial concerns (0-100, higher scores better) | 93.9 |
| | | | SQOL, skin irritation (0-100, higher scores better) | 70.5 |
| | | | SQOL, life satisfaction (0-100, higher scores better) | 90.8 |
| | | | Fazio (0–1, mean) | 0.9 |
| | | | CGQL, current QOL (0-10, higher scores better) | 9 |
| | | | CGQL, current health (0-10, higher scores better) | 8.8 |
| | | | CGQL, current energy (0-10, higher scores better) | 8 |

CGQL, Cleveland Global Quality of Life; DQO, Direct Questioning of Objections; EQ, EuroQOL; EQ-5D, EuroQOL 5 dimensions; FIQL, Fecal Incontinence Quality of Life Scale; IBDQ, Inflammatory Bowel Disease Questionnaire; NR, not reported; QOL, quality of life; SF-36, Short-Form 36; SIBDQ, Short Quality of Life in Inflammatory Bowel Disease Questionnaire; SIP, Sickness-Impact Profile; SQOL, Stoma Quality of Life Scale; TTOT, Time Trade-Off Technique; VAS, visual analog scale

The above findings support a Low certainty conclusion that most have good quality of life, health status, or health-related quality of life after PC with IPAA, with downgrades for risk of bias and imprecision (results not reported in sufficient detail to permit assessment of precision).

### *Evidence Synthesis Process for FAQ 3*

| Outcome | Approach taken and justification | Results |
|---|---|---|
| Quality of life and symptoms | **Preponderance of evidence, qualitative expression**. Given the variety of ways in which the global construct of quality of life was assessed, providing a quantified result is not considered appropriate. Although some studies reported the percentage of people reporting improvement or satisfaction, we consider it inappropriate to selectively use these studies to provide quantified estimates. Some studies give results that allow inference that quality of life improved with PC with IPAA, either by directly assessing people before and after PC with IPAA or by using questionnaires or other methods that permit insight into how quality of life changed after PC with IPAA. Some studies only report quality of life on a continuous scale after PC with IPAA without any clear indication of these people's quality of life prior to PC with IPAA. However, even these studies seem to report high quality of life ratings overall, and this seems incompatible with what would be expected from someone suffering from medication-refractory or near-medication-refractory ulcerative colitis. So, albeit indirectly, even these studies seem consistent with an inference that quality of life improves (or at the very least is good) after PC with IPAA. In summary, the global pattern of results offers a consistent signal of people reporting good/improved quality of life and satisfaction after PC with IPAA. The results from Heikens 2012 support a Moderate certainty conclusion, and the results from Murphy 2015 support a Low certainty conclusion, and they are consistent with each other. Therefore, we consider the totality of evidence to support a Moderate certainty conclusion. For simplicity in synthesis, we present the findings as improvement in quality of life and symptoms, which we feel is supported by the variety of outcomes presented in the above tables. We also note (as also noted by Heikens 2012) the full effects of PC with IPAA may take several months to manifest, perhaps up to 9 to 12 months. We feel this is important to inform patients about, so we include this in our synthesis statement as well. | **People usually have improvement in their quality of life after surgery. But it may take up to a year for the full benefits of the surgery to occur.** (Moderate certainty) |

### *Evidence Synthesis for FAQ 3*

**Overall, people usually have improvement in their quality of life after surgery. But it may take up to a year for the full benefits of the surgery to occur.** (Moderate certainty)

## Continued pharmacologic therapy

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

As stated in Part 1 Scoping, the population in consideration is heterogeneous and there are many medications that might still be available for any given patient with refractory ulcerative colitis; therefore, comparable to the situation for symptoms (FAQ 2), we cannot say whether quality of life will get better, stay the same, or get worse, but we can say there may be other medications a patient can try before pursuing surgery. We can also likely say that any impact on quality of life will likely be tied directly to how/if symptoms change.

### *Descriptive Summary Results for FAQ 3*

**Your quality of life may improve, stay the same, or get worse. This will likely depend on if your symptoms improve, stay the same, or get worse (see "What will my symptoms be?").**

## FAQ 4: What is my risk of developing colorectal cancer?

### Proctocolectomy with ileal pouch anal anastomosis

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

This surgery effectively eliminates a person's risk of colorectal cancer, though there is a rare chance s/he may develop adenocarcinoma of the cuff/pouch (Selvaggi 2014).

***Descriptive Summary Results for FAQ 4***

**People having this surgery cannot get cancer in the colon anymore, because the surgery removes the colon. Rarely, a person might get cancer in the pouch.**

## Continued pharmacologic therapy

Evidence concerning the risk of colorectal cancer in people with UC comes from a systematic review and meta-analysis that investigated the risk in several ways (Castaño-Milla 2014). The authors reported the cumulative incidence of colorectal cancer as the number of cases of colorectal cancer over the entire follow-up period per 1,000 people and the incidence rate of colorectal cancer as the number of cases of colorectal cancer per 1,000 person-years.
***Evidence Review Tables for FAQ 4***

**Estimates of cumulative incidence and incidence rate of colorectal cancer in people with UC for all studies and varies subgroups**

| Study or population type | No. studies (no. people; no. person-years) | Outcome | Estimate | Certainty |
|---|---|---|---|---|
| All studies | 81 (181,923; 1,570,936) | Cumulative incidence | 15.6/1,000 people (95%CI 13.8 to 17.4) | Very low[1,2,3] |
| | | Incidence rate | 1.58 per 1,000 person-years (95% CI 1.39 to 1.76) | Very low[1,2,3] |
| Population-based studies | 19 (67,141; 926,755) | Cumulative incidence | 13.3/1,000 people (95% CI 10.9 to 15.6) | Low[1,3] |
| | | Incidence rate | 1.24/1,000 person-years (95% CI 1.01 to 1.47) | Low[1,3] |
| Referral centers (mostly) | 62 (114,782; 644,181) | Cumulative incidence | 17.9/1000 people (95% CI 15.3 to 20.5) | Low[1,2] |
| | | Incidence rate | 1.9/1000 person-years (95% CI 1.63 to 2.18) | Low[1,2] |
| Studies assessing risk by duration of UC | 19 (not reported; not reported) | Incidence rate (cumulative incidence not reported) | First decade: 0.91/1,000 person-years (95% CI 0.61 to 1.2)<br><br>Second decade: 4.07/1,000 person-years (95% CI 2.58 to 5.56)<br><br>Third decade: 4.55/1,000 person-years (95% CI 2.64 to 6.46) | Low[1,3] for first decade<br><br>Very low[1,2,3] for second and third decades |

1, Serious concern for risk of bias
2, Serious concern for inconsistency
3, Serious concern for indirectness

**Estimates of cumulative incidence and incidence rate of colorectal cancer in people with UC based on year of publication**

| Group of studies based on decade of publication | No. studies (no. people)* | Cumulative incidence per 1,000 people (95% CI) | Incidence rate per 1,000 person-years (95% CI) | Certainty |
|---|---|---|---|---|
| 1950s | 3 (4,759; not reported) | 33.15 (0.58 to 65.73) | 4.29 (0.95 to 7.64) | Very low[1,2,3] |
| 1960s | 7 (19,304; not reported) | 31.43 (20.21 to 42.65) | 4.18 (2.67 to 5.68) | Very low[1,2,3] |
| 1970s | 4 (12,909; not reported) | 29.47 (2.47 to 56.37) | 3.22 (0.67 to 5.77) | Very low[1,2,3] |
| 1980s | 14 (123,866; not reported) | 31.37 (20.36 to 42.38) | 2.58 (1.81 to 3.34) | Very low[1,2,3] |
| 1990s | 12 (87,499; not reported) | 15.59 (9.6 to 21.57) | 1.53 (1.06 to 2) | Very low[1,2,3] |
| 2000s | 23 (369,829; not reported) | 14.26 (10.47 to 18.05) | 1.29 (1 to 1.58) | Very low[1,2,3] |
| 2010 to 2013 | 18 (861,478; not reported) | 9.05 (6.8 to 11.3) | 1.21 (0.95 to 1.48) | Very low[1,2,3] |

* Person-years of follow-up not reported for these analyses

1, Serious concern for risk of bias

2, Serious concern for inconsistency

3, Serious concern for indirectness

***Evidence Synthesis Process for FAQ 4***

| Outcome | Approach taken and justification | Results |
|---|---|---|
| Overall risk of colorectal cancer | **Meta-analysis already done**. Castaño-Milla 2014 provide meta-analytic estimates of the incidence rate for all studies, for population-based studies, and for (mostly) referral center-based studies. All these estimates are broadly consistent with each other: 1.58 per 1,000 person-years (95% CI 1.39 to 1.76), 1.24/1,000 person-years (95% CI 1.01 to 1.47), and 1.9/1000 person-years (95% CI 1.63 to 2.18), respectively. Considering all these together, there is a general pattern of about 1 to 2/1,000 person-years. Regardless of whether one uses these values with a linear or exponential function, the estimated 10-year risk would be about 1% to 2%. | **Overall 10-year risk is about 1% to 2%** (Low certainty) |
| Risk of colorectal cancer by duration of UC | **Meta-analysis already done.** Castaño-Milla 2014 provide meta-analytic estimates of the incidence rate for the first, second, and third decades of UC. The first decade has an incidence rate comparable to the incidence rates discussed for the outcome of "Overall risk of colorectal cancer", translating to a 10-year risk of about 1%. The second and third decades have higher incidence rates, and the risk of colorectal cancer may be influenced by the duration of the disease due to increased time that the bowel is exposed to inflammation. This is a key consideration behind the recommendations to start screening people with UC a certain number of years after they are diagnosed; additionally, although Lutgens 2013 was not progressed to Part 4 (for reasons stated in Part 3), they noted this trend as well. The second and third decades have similar incidence rates: 4.07 and 4.55 per 1,000 person-years, respectively. Considering these values with both a linear and exponential function suggests the estimated risk would be about 4% in the second decade and about 4% to 5% in the third decade. | **Risk in first, second, and third decades is about 1%, about 4%, and about 4 to 5%, respectively.** (Low certainty for first decade, Very low certainty for second and third decades) |
| Risk of colorectal cancer in contemporary era | **Meta-analysis already done**. Castaño-Milla 2014 provide meta-analytic estimates of the incidence rate for colorectal cancer stratified by decade of publication, and there seems to be a clear trend of decreasing risk in the more contemporary studies. Although Lutgens 2013 was not progressed to Part 4 (for reasons stated in Part 3), they noted this trend as well. Regardless of whether one uses these values with a linear or exponential function, the estimated 10-year risk would be about 1% if considering the most contemporary data. | **10-year risk in the most contemporary data is about 1%** (Very low certainty) |

Considering the above outcomes together, a global synthesis would suggest that the 10-year risk is – at its highest – about 4% to 5% after 20 to 30 years of having UC. However, although risk may indeed be higher in people who have had UC longer, the available data do not permit insight into how this might be reflected in more contemporary data. In other words, the estimate of 4% to 5% may be an overestimate due to the potential for older studies to upwardly bias the estimate even in the presence of a trend toward increased risk with longer disease duration. Additionally, focusing only on the risk over the first 10 years (which is functionally the same risk as the risk if considering all studies, the population-based studies, or the referral center-based studies) may be less meaningful for the intended population of this evidence report, as it is likely they are at least partially through the first decade. To address these considerations, one could either combine the risks for the first (1%), second (4%), and third decades (4% to 5%) to give an overall 30-year estimate of 9% to 10% or present the risks stratified by decade. Because it may be difficult for people to appreciate risks over a 30-year period, we have adopted the latter approach. We also state estimates for the second and third decades with "up to" in an attempt to emphasize these results are upper bounds and the true risk may be lower. Lastly, we also mention, for completeness, that the risk of colorectal cancer may be influenced by other factors as well, such as family history or comorbid primary sclerosing cholangitis (Kucharzik 2019).

### *Evidence Synthesis Results for FAQ 4*

**Your risk of getting cancer in the colon or rectum depends on several things. This includes things like if you also have primary sclerosing cholangitis or a family history of cancer in the colon or rectum. Additionally, the risk of getting cancer in the colon or rectum may go up the longer you have had ulcerative colitis.** (Low to Very low certainty evidence from 1 systematic review and meta-analysis [Castaño-Milla 2014])

**Of 100 people who continue taking medication:**

- **if they have had ulcerative colitis for 10 years or less, 1 to 2 (1% to 2%) may get cancer in the colon or rectum in the next 10 years** (Low certainty)
- **if they have had ulcerative colitis for more than 10 years but less than 20 years, up to 4 (4%) may get cancer in the colon or rectum in the next 10 years** (Very low certainty)
- **if they have had ulcerative colitis for more than 20 years but less than 30 years, up to 5 (5%) may get cancer in the colon or rectum in the next 10 years** (Very low certainty)

## FAQ 5: Will I need to have colon cancer screenings?

### Proctocolectomy with ileal pouch anal anastomosis

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

Because PC with IPAA effectively eliminates a person's risk of colorectal cancer (see "FAQ 4: What is my risk of developing colorectal cancer?"), people having PC with IPAA do not have to have colorectal cancer screening.

***Descriptive Summary Results for FAQ 5***

**No**

### Continued pharmacologic therapy

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

Guidelines from the American College of Gastroenterology (ACG) and the German Society for Digestive and Metabolic Diseases (GSDMD) both agree that people with UC not limited to the rectum should start having regular colonoscopies after a certain number of years have passed from the time of their diagnosis (Kucharzik 2019, Rubin 2019). The ACG recommends starting 8 years after diagnosis, and the GSDMD recommends starting 6 to 8 years after diagnosis. The guidelines give mostly consistent recommendations about the frequency with which people should be screened, each noting that the frequency should be individualized based on a person's risk factors for colorectal cancer (e.g., in addition to the UC *per se*, the degree of inflammation present in the colon and whether the person has numerous pseudopolyps or a first-degree relative who was diagnosed with colorectal cancer earlier than 50 years of age). The GSDMD gives a range of 1 to 4 years, and the ACG gives a range of 1 to 3 years. However, given the likelihood that this population has high-risk features (e.g., extensive and severe inflammation), many will likely be screened annually.

***Descriptive Summary Results for FAQ 5***

**Yes. People with ulcerative colitis usually start having colonoscopies 6 to 8 years after they are first diagnosed. Depending on a person's risk factors, the colonoscopies may be done every 1 to 4 years. However, many people will likely get a colonoscopy every year.**

## FAQ 6: What are the side effects or risks?

### Proctocolectomy with ileal pouch anal anastomosis

Evidence concerning the risks of having proctocolectomy with IPAA comes from a systematic review without meta-analysis (Peyrin-Biroulet 2016). Peyrin-Biroulet 2016 reported results as ranges rather than meta-analytic estimates; they did not perform meta-analyses due to "marked" heterogeneity.

#### *Evidence Review Tables for FAQ 6*

**Short-term (≤30 days) and long-term (>30 days) risks**

| Outcome | No. studies (no. people) | Range (no. events/sample size [%] for study with lowest and highest rate) | Certainty |
|---|---|---|---|
| Any infectious complication | 8 (1,134) | ≤30 days: 25/254 (10%) to 44/98 (45%) | Very low[1,2] |
| Pouchitis | 4 (946) | >30 days: 1/12 (8%) to 237/576 (41%) | Very low[1,2] |
| Pouch loss/failure/excision | 2 (239) | >30 days: 0%* to 2/12 (17%) | Very low [1,2] |
| Fistula | 1 (430) | ≤30 days: 0%* to 3/48 (6%)<br>>30 days: 0%* to 4/48 (8%) | Very low[1,2,3] |
| Small bowel obstruction | 6 (943) | ≤30 days: 1/61 (2%) to 8/68 (12%)<br>>30 days: 30/179 to 58/332 (both round to 17%) | ≤30 days: Very low[1,2]<br>>30 days: Moderate[1] |
| Anastomotic leak | 3 (1,608) | ≤30 days: 1/199 (0.5%) to 5/52 (10%) | Very low[1,2] |
| Pelvic sepsis or pelvic abscess | 5 (1,941) | ≤30 days: 0/19, 0/27, and 0/199 (0%)* to 9/48 (19%) | Very low[1,2,4] |
| Ileus | 4 (458) | ≤30 days: 7/51 (14%) to 6/20 (30%)<br>>30 days: 3/106 (3%) to 17/68 (25%) | ≤30 days: Very low[1,2,4]<br>>30 days: Very low[1,2] |
| Fecal incontinence | 1 (179) | >30 days: 15/73 (21%) to 23/106 (22%) | Low[1,3] |
| Mortality | 11 (5,196) | ≤30 days: 0%* to 16/559 (3%) | Low[1,4] |

1, Serious concern for risk of bias

2, Very serious concern for imprecision (either very serious concern with the imprecision of the range itself *or* serious concern with the imprecision of the range *plus* serious concern that at least one of the bounds of the range also suffered from serious imprecision, such as an estimate based on 2 events in 12 people). Accordingly, we assigned 2 downgrades.

3, Serious concern for inconsistency (due to only having one study reporting this outcome, thus precluding assessment of consistency of results)

4, Serious concern for indirectness (population informing estimate not sufficiently matched to population of interest for this evidence report, or concern over degree of match)

* Denominators were not reported for 0% risk estimates other than for pelvic sepsis or pelvic abscess. Three different cohorts had 0% risks for pelvic sepsis or pelvic abscess, so each is reported (0/19, 0/27, 0/199).

*Evidence Synthesis Process for FAQ 6*

| Outcome | Approach taken and justification | Results |
|---|---|---|
| Any infectious complication (≤30 days) | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. | **The risk of infection within 30 days of surgery may be 10% to 45%.** (Very low certainty) |
| Pouchitis | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. | **The risk of inflammation of the pouch at more than 30 days after surgery may be 8% to 41%.** (Very low certainty) |
| Pouch loss/failure/excision | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. The range provided is 0% to 17%, but the risk of 0% is implausible (i.e., some people are bound to have this happen), and the risk of 17% is based on a concerningly small number of events and people (2/12). Saying "up to 17%" would place too much emphasis on this number. Saying "0% to 17%" would incorporate the implausible value of 0% and might lead one to question why "up to" phrasing was not used. To address these issues, we report a range, but set the lower bound of the range as <1%, which we believe to be a reasonable compromise to reflect these nuances in a simple manner. | **The risk of the pouch not working or needing to be removed at more than 30 days after surgery may be <1% to 17%.** (Very low certainty) |
| Fistula | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. The same general concepts discussed for the outcome of "Pouch loss/failure/excision" apply here as well. | **The risk of a fistula within 30 days of surgery may be <1% to 6%. At more than 30 days after surgery, the risk may be <1% to 8%.** (Very low certainty) |
| Small bowel obstruction | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. | **The risk of a small bowel obstruction within 30 days of surgery may be 2% to 12%.** (Very low certainty) **At more than 30 days after surgery, the risk may be 17%.** (Moderate certainty) |

For the outcome of pouchitis, we also note this is often treated with antibiotics.

| | | |
|---|---|---|
| Anastomotic leak | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. | **The risk of an anastomotic leak within 30 days of surgery may be <1% to 10%.** (Very low certainty) |
| Pelvic sepsis or pelvic abscess | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. The same general concepts discussed for the outcome of "Pouch loss/failure/excision" apply here as well. Additionally, we note that pelvic abscess and pelvic sepsis, although both important, likely have considerably different degrees of importance to patients. With Peyrin-Biroulet 2016 not providing data for these outcomes separately and with the range being as broad as it is, we conclude that data are of insufficient quality to give numerical estimates. | **Some people may develop a pelvic abscess or pelvic sepsis after surgery, but we do not have enough information to know what the risk is.** (Very low certainty) |
| Ileus | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. | **The risk of ileus within 30 days of surgery may be 14% to 30%. At more than 30 days after surgery, the risk may be 3% to 25%.** (Very low certainty) |
| Fecal incontinence | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. | **The risk of fecal incontinence at more than 30 days after surgery may be 21% to 22%.** (Low certainty) |
| Mortality | **Systematic review already done, range of results.** The systematic review by Peyrin-Biroulet 2016 provides a range of risks. Although the upper bound estimate does not suffer as much as the other outcomes with respect to the number of events and people (16/559), we note that the outcome of mortality is likely considered extremely important by many people, so emphasizing only the upper bound would be potentially misleading, even with an absolute estimate as "small" as 3%. However, as noted in the discussion for the outcome of "Pouch loss/failure/excision", a 0% mortality rate is implausible, so we adopt the "<1%" method here as well. | **The risk of dying within 30 days of surgery may be <1% to 3%.** (Low certainty) |

For the outcome of ileus, we note this often resolves with conservative management by postoperative day 3. However, some cases may be prolonged. Although what constitutes "normal" postoperative ileus and "prolonged" postoperative ileus is nebulous, an international consensus panel proposed that prolonged ileus be considered ileus that lasts ≥4 days and is associated with ≥2 of: nausea or vomiting, inability to tolerate an oral diet over the previous 24 hours, no flatus over the previous 24 hours, abdominal distention, or radiologic confirmation (Vather 2013). We consider this a reasonable approach.

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

Patients may experience bowel changes after PC with IPAA as described in FAQ 2 "What will my symptoms be?".

Anastomotic leaks and instances of pouch failure may be lower with protective/diverting ileostomy, but anastomotic strictures may be higher (Weston-Petrides 2008). The choice of whether to have a protective/diverting ileostomy will be individualized for each person.

In line with guideline recommendations, because IPAA has been associated with fertility problems in both women and men, people interested in having children may wish to avoid IPAA and instead consider alternative surgical options or continued pharmacologic therapy (Kucharzik 2019, Waljee 2006, Rajaratnam 2011, Lee 2019).

Although the psychological (fear of stool leakage) and/or neurological (disruption of the autonomic nervous supply to the pelvic organs) impact of the surgery may result in at least short-term sexual dysfunction in some people, people may often find there is either no decrease or even an increase in their sexual satisfaction after surgery, which may be the result of feeling like their health is better overall (Cornish 2007, Crohn's and Colitis Foundation of America nd, UCSF Health nd).

### *Evidence Synthesis and Descriptive Summary Results for FAQ 6*

**People may have changes in their bowel movements after this surgery (see "What will my symptoms be?").**

**A woman or man who has this surgery may have a harder time getting pregnant with his/her partner. People planning on getting pregnant with their partner may want to consider a different surgery or continue to take medication to manage their symptoms.**

**After surgery, some people may have at least short-term problems with sex, but people may often find they are just as satisfied or more satisfied with their sex life.**

**Risks from having the surgery can be early (within 30 days of the surgery) or later (more than 30 days after the surgery).**

**Early risks** (all evidence from 1 systematic review without meta-analysis [Peyrin-Biroulet 2016], all Very low certainty unless stated otherwise)
**Of 100 people who have surgery:**

- **10 to 45 (10% to 45%) may get an infection**
  - **In some cases, the infection may be serious. We do not have enough information to know how often this occurs.**
- **14 to 30 (14% to 30%) may have their intestines stop moving. This often gets better within 3 days. Sometimes it lasts longer and may need more treatment to fix.**
- **2 to 12 (2% to 12%) may have their intestines get blocked, which may need more surgery to fix**
- **<1 to 6 (<1% to 6%) may get a connection between two parts of the body that is not normal (often called a "fistula"). This could be a connection between different parts of the intestines, between the intestines and the bladder, between the intestines and the skin, or some other combination.**
- **<1 to 10 (<1% to 10%) may have leaking at the point where the surgeon joined their intestines together**
- **<1 to 3 (<1% to 3%) may die** (Low certainty)

**Later risks** (all Very low certainty unless stated otherwise)
**Of 100 people who have surgery:**

- **3 to 25 (3% to 25%) may have their intestines stop moving. This often gets better within 3 days. Sometimes it lasts longer and may need more treatment to fix.**
- **17 (17%) may have their intestines get blocked, which may need more surgery to fix** (Moderate certainty)
- **8 to 41 (8% to 41%) may have infection or inflammation of their pouch, which is often treated with antibiotics**
- **<1 to 17 (<1% to 17%) may have their pouch not work or need to have their pouch removed**
- **<1 to 8 (<1% to 8%) may get a connection between two parts of the body that is not normal (often called a "fistula")**
- **21 to 22 (21% to 22%) may have times when they cannot control when they have a bowel movement** (Low certainty)

**If the surgeon also does something called a "protective ileostomy" or "diverting ileostomy", this may:**

- **lower the risk of leaking at the point where the intestines are joined together**
- **lower the risk of the pouch not working**
- **increase the risk of part of the intestines becoming too small**

## Continued pharmacologic therapy

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

As stated in Part 1 Scoping, the population in consideration is heterogeneous and there are many medications that might still be available for any given patient with refractory ulcerative colitis; therefore, we do not aim to provide a comprehensive account of all possible side effects or risks here, but rather, a sampling of common side effects and the most common and serious risks for various pharmacologic options.

Examples of side effects from medication include, but are not limited to:

- azathioprine and its metabolite 6-mercaptopurine: nausea and vomiting
- cyclosporine: gingival hyperplasia, headache, tremor, hirsutism – not noted in summary answer because cyclosporine is used less often
- anti-TNF agents (infliximab, adalimumab, golimumab): injection site pain, chest pain, rash, gastrointestinal symptoms (abdominal pain, nausea), headache, upper respiratory symptoms (cough, pharyngitis, sinusitis, upper respiratory infection), fatigue, dyspnea, dizziness, paresthesias
- anti-integrin agent (vedolizumab): nausea, arthralgia, headache, upper respiratory symptoms (nasopharyngitis, upper respiratory infection), fatigue
- systemic corticosteroids: fluid retention, increased appetite and weight gain, mood swings

Although serious risks from medication may be uncommon, examples of risks include, but are not limited to:

- azathioprine and its metabolite 6-mercaptopurine: hypersensitivity reaction, acute pancreatitis, hepatitis, malignancy (e.g., myeloproliferative disorders, nonmelanoma skin cancers), bone marrow suppression/myelotoxicity
- cyclosporine: hypertension, electrolyte disturbances, encephalopathy, progressive multifocal leukoencephalopathy, seizure, nephrotoxicity, infection, lymphoma
- anti-TNF agents (infliximab, adalimumab, golimumab): infection, heart failure, hypertensive encephalopathy, syncope, hypersensitivity reaction, myelosuppressive disorders, erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis, lymphoma, hepatitis, hypertension, cardiac dysrhythmias
- anti-integrin agent (vedolizumab): hepatitis, hypersensitivity reaction, progressive multifocal leukoencephalopathy, infection

Additionally, we note people's perioperative risk may be increased by continuing with prolonged medication therapy, and given the inflammation of the UC may continue unabated, they are also at risk for complications from continued UC disease activity (e.g., perforation, stenosis, toxic megacolon).

(DynaMed 2018, Kucharzik 2019, Rubin 2019)

***Descriptive Summary Results for FAQ 6***

**Side effects and risks from medication depend on the medication that might be tried.**

**Side effects from medication may include:**

- **nausea, vomiting, or stomach pain**
- **cough, shortness of breath, upper respiratory infection, or pain in the chest**
- **fatigue, headache, or dizziness**
- **numbness, pain, tingling, or strange feelings in different parts of the body**
- **joint pain**
- **increased appetite and weight gain**
- **mood changes**
- **injection site pain (if the medicine is injected)**

**Although serious risks from medication may be uncommon, risks might include:**

- **infection and decreased ability to fight infection**
- **decreased ability to make important parts of blood (red blood cells, white blood cells, and/or platelets)**
- **heart failure or bad heart rhythms**
- **passing out**
- **pancreatitis or hepatitis**
- **severe allergic reaction**
- **severe rash, which can be life-threatening in its worst form**
- **certain cancers, such as lymphoma**
- **serious problems in the brain from increased blood pressure or a virus, which may or may not be reversible and can cause death**

**People who continue to take medicine still have the bad part of the intestines inside them. Because of this, there is a risk the intestines could:**

- **get too small in certain areas**
- **get a tear in them, which is an emergency**
- **get dangerously large in certain areas, which is an emergency**

**Although patients who continue to take medicine can decide to have surgery later, they may have more risks from surgery than people who have surgery earlier.**

**Patients can discuss possible side effects and risks in more detail with their clinician.**

## FAQ 7: When will I recover?

This FAQ only applies for the option of PC with IPAA.

### Proctocolectomy with ileal pouch anal anastomosis

**Descriptive Summary (pre-synthesis and synthesis efforts not applicable for descriptive summaries)**

For about 6 to 8 weeks after surgery, people may be advised to avoid certain foods, like raw fruits and vegetables, seeds, and nuts. For about 4 to 6 weeks after surgery, people may be advised to avoid lifting and strenuous activity. For some people, the surgeon may recommend a longer period of activity restriction. Most people can return to work and normal activities about 4 to 8 weeks after surgery; this includes sex, which might be resumed around 6 weeks. Timelines for each person should be individualized.

(See FAQ 1 for references)

***Descriptive Summary Results for FAQ 7***

**For about 6 to 8 weeks after surgery, people may be advised to avoid certain foods. Most people can return to the things they normally do in about 4 to 8 weeks, including work and sex. Each person should talk with the surgeon about when it is okay to return to certain activities.**

# Evidence report for ulcerative colitis refractory to medication therapy

## Part 2 - Search and Selection

Prepared by EBSCO Information Services

October 14, 2019

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# Abbreviations

## General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IQR – interquartile range
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SD – standard deviation
SE – standard error
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

## Abbreviations specific to this report that may appear in this report

IBD – inflammatory bowel disease
IPAA – ileal pouch anal anastomosis (sometimes also referred to as ileoanal pouch anastomosis)
PC – proctocolectomy
UC – Ulcerative colitis

**Note**: PC with IPAA is sometimes referred to as restorative proctocolectomy. We standardize on the term PC with IPAA throughout.

# Methods

First-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews or guidelines that involve a systematic review that are more recent than those identified in first-round searching.

Third-round searching will involve original study tracing from systematic reviews, guidelines or other relevant sources. This may be done to identify additional evidence sources if the results from the first two rounds of searching are insufficient.

Fourth-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

Additional evidence updates may also be added continuously from feedback from any source.

## FAQ Summary

# Results

## First-round searching – DynaMed:

| DynaMed subsection | Number of article citations | Number of unique references included |
|---|---|---|
| Ulcerative Colitis in Adults topic, Management section, Surgery and procedures subsection, Surgical procedures subsection, Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) subsection | 7 | 0 |
| Ulcerative Colitis in Adults topic, Complications and Prognosis section, Complications subsection, Cancer subsection | 16 | 1 (Lutgens 2013) |

## Second-round searching – searches for intervention-specific systematic reviews:

| Database | Search string | Number of search results | Number of references included |
|---|---|---|---|
| PubMed October 14, 2019 | (colectomy[tiab] OR proctocolectomy[tiab]) AND (ulcerative colitis[tiab] OR inflammatory bowel disease[tiab]) AND (quality of life[tiab]) AND systematic[sb] | 16 | 2 (Murphy 2015, Heikens 2012) |
| PubMed October 14, 2019 | (colectomy[tiab] OR proctocolectomy[tiab]) AND (ulcerative colitis[tiab] OR inflammatory bowel disease[tiab]) AND complication*[tiab] AND systematic[sb] | 26 | 1 (Peyrin-Biroulet 2016) |
| PubMed October 15, 2019 | colorectal cancer[ti] AND (ulcerative colitis[ti] OR inflammatory bowel disease[ti] OR IBD[ti]) AND (systematic[sb] OR meta-analysis[pt]) AND ("2013/01/01"[PDAT] : "3000/12/31"[PDAT]) | 17 | 3 (Castaño-Milla 2014, Lutgens 2013*, Wheat 2016) |

* already captured in first-round searching

## **Third-round searching** – study tracing from systematic reviews:

| Source | Tracing | Number of search results | Number of references included |
|---|---|---|---|
| Not applicable | | | |

## Fourth-round searching – searches for original evidence reports:

| Database | Search string | Number of search results | Number of references included |
|---|---|---|---|
| Not applicable | | | |

## Search summary:

**Number of articles screened and selected**

| | Screened | Selected* |
|---|---|---|
| **1st-round (DynaMed)** | 23 | 1 |
| **2nd-round (Systematic review searches)** | 59 | 5 |
| **3rd-round (Study tracing)** | Not applicable | |
| **4th-round (Original article searches)** | Not applicable | |
| ***Total*** | *82* | *6* |

* Number shown is after deduplication

| | Articles selected for evaluation (Author Year) |
|---|---|
| **Systematic reviews** | 6 (Castaño-Milla 2014, Heikens 2012, Lutgens 2013, Murphy 2015, Peyrin-Biroulet 2016, Wheat 2016) |
| **Randomized, controlled trials** | 0 |
| **Other article types** | 0 |

# Evidence report for ulcerative colitis refractory to medication therapy

## Part 3 - Critical Appraisal of Evidence Reports

Prepared by EBSCO Information Services

October 14, 2019

Prepared by EBSCO Health Innovations and EBM Development Department:

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# Abbreviations

## General abbreviations that may appear in this report

CI – confidence interval
CrI – credible interval
HR – hazard ratio
IQR – interquartile range
MA – meta-analysis
MD – mean difference
NA, N/A – not applicable
NR – not reported
OR – odds ratio
RCT – randomized, controlled trial
RR – risk ratio, relative risk
RtR – rate ratio
SD – standard deviation
SE – standard error
SMD – standardized mean difference
SR – systematic review
SRMA – systematic review and meta-analysis

## Abbreviations specific to this report that may appear in this report

IBD – inflammatory bowel disease
IPAA – ileal pouch anal anastomosis (sometimes also referred to as ileoanal pouch anastomosis)
PC – proctocolectomy
UC – Ulcerative colitis

**Note**: PC with IPAA is sometimes referred to as restorative proctocolectomy. We standardize on the term PC with IPAA throughout.

## Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.
-

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

## FAQ Summary

# Results

## Characteristics and Results of Critically Appraised Studies/Sources

***For the certainty statements for this evidence report, comparative data are lacking, so all certainty statements refer to univariate or prognostic estimates only.***

**CASTAÑO-MILLA 2014**

Castaño-Milla C, Chaparro M, Gisbert JP. Systematic review with meta-analysis: the declining risk of colorectal cancer in ulcerative colitis. Aliment Pharmacol Ther. 2014 Apr;39(7):645-59. PubMed

Relevant to FAQ4

- **Study design:** systematic review of observational studies
- **Population:** people with UC
- **Intervention:** not applicable
- **Comparison:** not applicable

- **Study inclusion criteria:**
  - described incidence rate of colorectal cancer and follow-up time (or enough information to calculate these data) for people with UC (studies only providing data for people with inflammatory bowel disease as a global group were excluded)

- **Number of studies:** 81
  - 19 were population-based; 62 were mainly cohort studies from referral centers
- **Number of participants:** 181,293
  - 67,141 from population-based studies
- **Duration of follow-up:** 1,570,936 person-years of follow-up overall; 926,755 person-years of follow-up for population-based studies
  - all follow-up durations for the individual studies were reported in person-years, but all results are presented as incidence rates (some results are also presented as cumulative incidence)
  - study-level person-years of follow-up: range 101 to 274,185; mean 19,394; median 4,901

- **Results and Certainty:**

**Estimates of cumulative incidence and incidence rate of colorectal cancer in people with UC for all studies and varies subgroups**

| Study or population type | No. studies (no. people; no. person-years) | Outcome | Estimate | Certainty |
|---|---|---|---|---|
| All studies | 81 (181,923; 1,570,936) | Cumulative incidence | 15.6/1,000 people (95% CI 13.8 to 17.4) | Very low[1,2,3] |
| | | Incidence rate | 1.58 per 1,000 person-years (95% CI 1.39 to 1.76) | Very low[1,2,3] |
| Population-based studies | 19 (67,141; 926,755) | Cumulative incidence | 13.3/1,000 people (95% CI 10.9 to 15.6) | Low[1*,3] |
| | | Incidence rate | 1.24/1,000 person-years (95% CI 1.01 to 1.47) | Low[1*,3] |
| Referral centers (mostly) | 62 (114,782; 644,181) | Cumulative incidence | 17.9/1000 people (95% CI 15.3 to 20.5) | Low[1,2] |
| | | Incidence rate | 1.9/1000 person-years (95% CI 1.63 to 2.18) | Low[1,2] |
| Studies assessing risk by duration of UC | 19 (not reported; not reported) | Incidence rate (cumulative incidence not reported) | First decade: 0.91/1,000 person-years (95% CI 0.61 to 1.2)<br><br>Second decade: 4.07/1,000 person-years (95% CI 2.58 to 5.56)<br><br>Third decade: 4.55/1,000 person-years (95% CI 2.64 to 6.46) | Low[1†,3] for first decade<br><br>Very low[1,2,3] for second and third decades |
| Only extensive UC | 8 (1,785; not reported) | Cumulative incidence | 44.4/1,000 people (95% CI 22.8 to 66) | Very low[1,2,3] |
| | | Incidence rate | 4.02/1,000 person-years (95% CI 2.74 to 5.31) | Very low[1,2,3] |

1, Serious concern for risk of bias for all outcomes given the mean, median, and mode of the Newcastle-Ottawa Scale were each 6 (0 to 9 scale, higher scores are better); only 13/81 studies had Newcastle-Ottawa Scale scores >6, and authors only provide a summary table in an appendix based on the study, not based on the outcome assessed
2, Serious concern for inconsistency given heterogeneity present and/or insufficient information provided to adequately assess heterogeneity; the authors provide statistical tests for heterogeneity such as the $I^2$, but this is typically insufficient to adequately assess heterogeneity (this can be especially true for univariate estimates in large datasets)
3, Serious concern for indirectness as it is unclear to what extent this estimate accurately reflects the risk in people with refractory UC. This includes the extensive colitis estimates, as the extent of colonic involvement does not necessarily indicate whether the person has refractory colitis, and vice versa. We did not apply an indirectness downgrade for estimates from studies mostly from referral centers, as there is a substantial chance these estimates are largely comprised of people with refractory UC.
* Because there was no serious concern for inconsistency for the incidence rate, we did not assign a downgrade for inconsistency for the cumulative incidence despite the authors only reporting statistical tests for heterogeneity for cumulative incidence (and not a forest plot)
† Although statistical testing by itself is typically inadequate to fully assess the consistency of results, the authors report an $I^2$ of 0%, which in this setting might be reasonably taken as evidence of no serious inconsistency (the concern with relying on $I^2$ for assessing heterogeneity of univariate estimates, especially when working with larger datasets, is the possibility of the $I^2$ incorrectly suggesting serious inconsistency)

**Estimates of cumulative incidence and incidence rate of colorectal cancer in people with UC based on year of publication**

| Decade of publication | No. studies (no. people)* | Cumulative incidence per 1,000 people (95% CI) | Incidence rate per 1,000 person-years (95% CI) | Certainty |
|---|---|---|---|---|
| 1950s | 3 (4,759) | 33.15 (0.58 to 65.73) | 4.29 (0.95 to 7.64) | Very low[1,2,3] |
| 1960s | 7 (19,304) | 31.43 (20.21 to 42.65) | 4.18 (2.67 to 5.68) | Very low[1,2,3] |
| 1970s | 4 (12,909) | 29.47 (2.47 to 56.37) | 3.22 (0.67 to 5.77) | Very low[1,2,3] |
| 1980s | 14 (123,866) | 31.37 (20.36 to 42.38) | 2.58 (1.81 to 3.34) | Very low[1,2,3] |
| 1990s | 12 (87,499) | 15.59 (9.6 to 21.57) | 1.53 (1.06 to 2) | Very low[1,2,3] |
| 2000s | 23 (369,829) | 14.26 (10.47 to 18.05) | 1.29 (1 to 1.58) | Very low[1,2,3] |
| 2010 to 2013 | 18 (861,478) | 9.05 (6.8 to 11.3) | 1.21 (0.95 to 1.48) | Very low[1,2,3] |

* Person-years of follow-up not reported for these analyses
See above for numerical footnotes pertaining to Certainty statements

- **Other considerations**
  - not included in this summary are cumulative incidence and/or incidence rate (as applicable) for subgrouping of studies by surveillance program studies
  - the results for studies limited to extensive colitis are not carried forward to Part 4; as noted in the footnote for that outcome, a person having extensive colitis does not necessarily mean s/he has refractory colitis (and vice versa), so the subgroup of studies limited to those with extensive colitis is considered to be less relevant than the others presented in this summary

**HEIKENS 2012**
Heikens JT, de Vries J, van Laarhoven CJ. Quality of life, health-related quality of life and health status in patients having restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis: a systematic review. Colorectal Dis. 2012 May;14(5):536-44. doi: 10.1111/j.1463-1318.2010.02538.x. PubMed

Relevant to FAQ3

- **Study design:** systematic review of observational studies
- **Population:** adults with UC undergoing PC with IPAA
- **Intervention:** PC with IPAA
- **Comparison:** not applicable

- **Study inclusion criteria:**
  - measured quality of life, health-related quality of life, and/or health status
  - minimum follow-up duration of 12 months

    - despite stating this as the minimum, included two studies for which information on follow-up duration was not provided

- **Number of studies:** 33
    - 7 before and after IPAA, 26 after IPAA
    - 3 deemed high quality, 23 of moderate quality, and 7 of low quality
        - Based on 19 predefined criteria for assessing quality, with scores ≥ 75% (14/19) being high, between 50% and 75% moderate, and < 50% low
- **Number of participants:** 4,790
- **Duration of follow-up:** median 45 months (range 12 to 130 months)
    - 3 studies rated high quality all had follow-up durations of 12 months
    - median follow-up 51 months (range 12 to 130) among 23 studies rated moderate quality
    - median follow-up 33 months (range 28 to 96) among 7 studies rated low quality

- **Results:** no meta-analysis performed; results presented and synthesized narratively

**Study details and postsurgical results for health-related quality of life and/or health status for included studies**

| Study | Follow-up (months) | No. people | Did all have UC? | Quality rating (per Heikens 2012) | Outcome measured (after surgery unless stated otherwise) | Conclusion |
|---|---|---|---|---|---|---|
| McLeod et al | 12 | 37 | Yes | High | HRQoL | usually improves |
| Polle et al | 12 | 53 | No (19 did not have UC) | High | HS and HRQoL, before and after | both improve |
| Thirlby et al | 12 | 27 | Yes | High | HS, before and after | improves and is similar to the general population |
| Delaney et al | 55 | 1285 | Yes | Moderate | HRQoL | careful selection permits "acceptable" outcome |
| Hahnloser et al | 130 | 1885 | Yes | Moderate | HS, before and after | "is preserved" |
| Heuschen et al | 43 | 243 | No (58 did not have UC) | Moderate | HS | similar to the general population if there are no postoperative complications |
| Scarpa et al | 101 | 36 | Yes | Moderate | HS | medications, frequency of bowel movements, presence/absence of pouchitis, age at diagnosis, and postoperative complications all influence |
| Berndtsson and Oresland | 12 | 32 | Yes | Moderate | HS and HRQoL, before and after | no change |
| Carmon et al | 51 | 78 | Yes | Moderate | HS | similar to the general population |

| | | | | | | |
|---|---|---|---|---|---|---|
| Muir et al | 12 | 20 | Yes | Moderate | HS, before and after | improves |
| Robb et al | 45 | 138 | Yes | Moderate | HS | "increases … significantly" and is similar to the general population |
| Young et al | 68 | 48 | Yes | Moderate | HRQoL, before and after | poor in most |
| Camilleri-Brennan | 41 | 19 | Yes | Moderate | HS | high |
| Holubar and Hyman | 85 | 51 | Yes | Moderate | HS | "extremely well preserved" |
| Martin et al | 46 | 29 | Yes | Moderate | HS | similar to those "in remission or with mild symptoms" |
| Mowschenson et al | 75 | 111 | No (3 did not have UC)* | Moderate | HS | normal in most |
| Pace et al | 24 | 13 | Yes | Moderate | HS | "generally satisfying" |
| Weinryb et al | 82 | 40 | Yes | Moderate | HS | good |
| Coffey et al | 67 | 54 | Yes | Moderate | HRQoL | dietary choices and timing, preoperative diagnosis, and pregnancy all influence |
| Hauser et al | 80 | 61 | Yes | Moderate | HS | "also determined by anxiety and extra-intestinal manifestations" |
| O'Bichere et al | 13 | 30 | Yes | Moderate | HS | "improved pelvic function" leads to improvement |
| Richards et al | 48 | 56 | Yes | Moderate | HS and HRQoL | similar to the general population |
| Sagar et al | 12 | 103 | Yes | Moderate | HS | good |
| Seidel et al | 31 | 55 | No (20 did not have UC) | Moderate | HS | good, with most having an improvement |
| Steens et al | 67 | 36 | No (5 did not have UC) | Moderate | HS and HRQoL | "only slightly decreased" |
| Willis et al | 96 | 24 | Yes | Moderate | HS | "significantly better" if no major postoperative issues |
| Barton et al | 33 | 37 | Yes | Low | HS | good |
| Pezim and Nicholls | 28 | 51 | No (7 did not have UC) | Low | HS | satisfactory |
| Tiainen and Matikainen | 96 | 68 | Yes | Low | HS | similar to the general population |

| | | | | | | |
|---|---|---|---|---|---|---|
| Lecointe-Besancon et al | 31 | 13 | Yes | Low | HRQoL | "similar between continent and incontinent patients" |
| Brunel et al | 35 | 27 | Yes | Low | HRQoL, before and after | improved |
| Hildebrandt et al | NR | 5 | Yes | Low | HRQoL | 9/10 |
| Vendrell et al | NR | 25 | Yes | Low | HS | improved |

HRQoL, health-related quality of life; HS, health status (considered a subset of HRQoL); NR, not reported; UC, ulcerative colitis
* Heikens 2012's reporting for this study is somewhat unclear, but review of Mowschenson et al shows 130 people were included (127 with UC, 3 with familial adenomatous polyposis), but only 111 of 125 eligible people returning the questionnaire (only 125 were eligible due to 2 deaths and 3 pouch excisions).

- **Authors' qualitative synthesis of postsurgical outcomes:**
  - Authors considered results consistent if ≥75% of studies "showed the same trend"
  - High-quality studies (3 studies; 117 people, 98 with UC)
    - HRQoL and HS improve and are "indistinguishable from the general population"
  - Moderate-quality studies (23 studies; 4,423 people, 4,380 with UC)
    - HRQoL and HS improve and are "comparable with general levels in a health population"
  - Low-quality studies (7 studies; 226 people, 219 with UC)
    - HRQoL and HS improve and range "from satisfactory to good"

- **Certainty: Moderate** for statement that most have an improvement in health status or health-related quality of life after PC with IPAA
  - **Risk of bias:** No serious concern
    - Although only 3 small studies were rated as being high quality, their results are consistent with the results of the lower-quality studies that made up the preponderance of evidence in this systematic review
  - **Imprecision:** Serious concern
    - Results not reported in sufficient detail to assess precision of results
  - **Indirectness:** No serious concern
  - **Inconsistency:** No serious concern
    - Some studies reported no change, reductions, or only "preservation" of quality of life measures, but the vast majority of studies showed consistent findings of improvement

**LUTGENS 2013**
Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis. 2013 Mar-Apr;19(4):789-99. doi: 10.1097/MIB.0b013e31828029c0. PubMed

Although risk of colorectal cancer is the key outcome in FAQ 4, a full summary of this systematic review and meta-analysis was not prepared, because Castaño-Milla 2014 is specific to UC, whereas Lutgens 2013 is not. Additionally, Lutgens 2013 focus on what they called the "standardized incidence ratio", a relative estimate intended to capture the risk relative to a "background population [without UC] adjusted for age, gender, and disease duration"; however, they do provide some absolute estimates (e.g., Table 6, which provides cumulative risks and incidence rates based on disease duration). Lutgens 2013 also include less data than Castaño-Milla 2014. For instance, Lutgens 2013 include 9 population-based studies for people with UC totaling 11,636 people and 180,819 person-years of follow-up, whereas Castaño-Milla 2014 include 19 population-based studies totaling 67,141 people and 926,755 person-years of follow-up; the same is true for studies from referral centers (4 studies totaling 2,544 people and 33,679 person-years of follow-up vs. 62 studies totaling 114,782 people and 644,181 person-years of follow-up, respectively). Therefore, Lutgens 2013 is not carried forward to Part 4, though we note their finding of a decreasing risk of colorectal cancer in inflammatory bowel disease (even serving as its title) is consistent with Castaño-Milla 2014; their findings of risk being higher in people with longer disease duration and extensive disease are also consistent with Castaño-Milla 2014.

**MURPHY 2015**
Murphy PB, Khot Z, Vogt KN, Ott M, Dubois L. Quality of Life After Total Proctocolectomy With Ileostomy or IPAA: A Systematic Review. Dis Colon Rectum. 2015 Sep;58(9):899-908. doi: 10.1097/DCR.0000000000000418.PubMed

Relevant to FAQ3

- **Study design:** systematic review of observational studies
- **Population:** adults undergoing surgical treatment for UC
- **Intervention:** PC with IPAA
    - This is the relevant group for this evidence report
- **Comparison:** PC with ileostomy
    - Results for this group are not considered in this evidence report
- **Study inclusion criteria:**
    - measured some aspect of health-related quality of life

- **Number of studies:** 13
    - all observational: 2 prospective cohort studies, 11 retrospective cohort studies

  - the authors consider Camilleri-Brennan 2003 to be a "prospective case-control" study, but this is inaccurate; this study design best matches a retrospective cohort study with matching on certain variables (date of operation +/- 4 months, sex, age +/- 4 years, and socioeconomic status) and additionally, Camilleri-Brennan 2003 note that although operative complications and number of operative stages were captured prospectively for all people, health-related quality of life was only assessed "once, 1 year or more after the final operative stage", and the people included in the study had operations completed "at least 1 year prior to the study" (with the matched people possibly being +/- 4 months)
- **Number of participants:** 783
  - 1,603 total, but the above number is for the group receiving PC with IPAA (those receiving PC with ileostomy are not relevant for this evidence report)
- **Duration of follow-up:** 12 to 157 months

- **Results:** no meta-analysis performed; results presented and synthesized narratively

**Study details and postsurgical results for various quality of life measures in included studies, PC with IPAA group only***

| Study | No. people | Follow-up in months (mean unless otherwise specified) | Outcome | Results (% or mean value, unless stated otherwise) |
|---|---|---|---|---|
| Emblem et al | 19 | 48 | Social restriction | 0% |
| Pemberton et al | 298 | 47 (median) | Overall satisfaction | 95% |
| | | | Return to work/school | 98% |
| McLeod et al | 37 | NR | TTOT (0–1, higher scores better) | 0.95 |
| | | | DQO (0–1, higher scores better) | 0.87 |
| | | | SIP (0–100, lower scores better) | 1.2 |
| Liddell et al | 25 | 40 | Lifestyle satisfaction (1–7, higher scores signal more improvement) | 5.48 |
| Kartheuser et al | 29 | 41 | Well-being | 91% |
| | | | No social restriction | 86% |
| | | | No work restriction | 91% |
| | | | Overall satisfaction | 91% |
| Jimmo et al | 55 | 12 | IBDQ (32–224, higher scores better) | 205 |
| O'Bichere et al† | 30 | 13 | SF-36 (0–100, higher scores better) | 78 |
| Seidel et al | 55 | 31 (combined for IPAA and ileostomy groups) | Overall QOL better since operation (always) | 87% |

| | | | | |
|---|---|---|---|---|
| Nordin et al | 56 | NR | SF-36, social functioning (0–100, higher scores better)‡ | 70.2 |
| | | | IBDQ, bowel symptoms subscale (10-70, higher scores better)§ | 54.4 |
| | | | IBDQ, emotional function subscale (12-84, higher scores better)§ | 64.8 |
| Camilleri-Brennan et al | 19 | 41 (median) | SF-36 (0–100, higher scores better) | 85.9 |
| | | | IBDQ (transformed to a 0-100 scale, higher scores better) | 85.4 (median) |
| Wang et al¶ | 48 | 41 | SF-36, physical scale (0–100, higher scores better) | 55.5 |
| | | | SF-36, mental scale (0–100, higher scores better) | 55 |
| | | | IBDQ (32–224, higher scores better) | 181.1 |
| van der Valk et al | 77 | NR | EQ-5D index (0–1, higher scores better)** | 0.85 |
| Kuruvilla et al | 35 | 157 | EQ-5D index (0–1, higher scores better)** | 0.85 |
| | | | EQ VAS (0–100, higher scores better) | 85.4 |
| | | | SIBDQ (10–70; higher scores better)†† | 62.2 |
| | | | FIQL (1–4, higher scores better) | 3.7 |
| | | | SQOL, sexuality/body (0-100, higher scores better) | 93.1 |
| | | | SQOL, work/social function (0-100, higher scores better) | 93.4 |
| | | | SQOL, financial concerns (0-100, higher scores better) | 93.9 |
| | | | SQOL, skin irritation (0-100, higher scores better) | 70.5 |
| | | | SQOL, life satisfaction (0-100, higher scores better) | 90.8 |
| | | | Fazio (0–1, mean) | 0.9 |
| | | | CGQL, current QOL (0-10, higher scores better) | 9 |
| | | | CGQL, current health (0-10, higher scores better) | 8.8 |
| | | | CGQL, current energy (0-10, higher scores better) | 8 |

CGQL, Cleveland Global Quality of Life; DQO, Direct Questioning of Objections; EQ, EuroQOL; EQ-5D, EuroQOL 5 dimensions; FIQL, Fecal Incontinence Quality of Life Scale; IBDQ, Inflammatory Bowel Disease Questionnaire; NR, not reported; QOL, quality of life; SF-36, Short-Form 36; SIBDQ, Short Quality of Life in Inflammatory Bowel Disease Questionnaire; SIP, Sickness-Impact Profile; SQOL, Stoma Quality of Life Scale; TTOT, Time Trade-Off Technique; VAS, visual analog scale

* Numerous elements in this table required validation or clarification from the full-text article and/or scale in consideration (i.e., reporting in Murphy 2015 was suboptimal). The most important instances of this are included as footnotes to this table. Only group receiving PC with IPAA shown (other group not relevant).
† VAS scores not shown. Using a VAS scale from 1 (least problematic) to 10 (most problematic), people were to rate how problematic they considered "the surgery in relation to each domain" for the outcomes of body image (5), altered emptying (8), odor (5), noise (5.5), sexual relationship (5), clothes (3.5), and diet (5.5), with the intent to compare these scores to the scores for ileostomy
‡ Murphy 2015 notes other subscales not reported, but noted not to be statistically significantly different from those receiving ileostomy
§ Murphy 2015 reports mean scores for the bowel symptoms and emotional function subscales were not reported and that scores for the systemic symptoms and social function subscales were, but Murphy 2015 erroneously flipped these items (bowel symptoms and emotional function were reported, the other two were not). This is also apparent by the highest possible scores in each of the subscales of the IBDQ (70 for bowel symptoms, 35 for systemic symptoms and social function, and 84 for emotional function).
¶ Wang et al's results include people with UC or Crohn's, not just people with UC
** Murphy 2015 reports this as EQ-5D-3L, from which the EQ-5D index can be reported/determined; this is what van der Valk and Kuruvilla et al actually report.
†† Murphy 2015 reports this scale is from 0-100, but this is inconsistent with how the SIBDQ is scored (10 items scored from 1 to 7 each), and Kuruvilla et al give no indication of transforming/altering the SIBDQ.

- **Certainty: Low** for statement that most have good quality of life, health status, or health-related quality of life after PC with IPAA
  - **Risk of bias:** Serious concern
    - Only studies comparing PC with IPAA vs. PC with ileostomy were included, leading to a possible selection bias compared to the overall body of evidence for PC with IPAA
    - Assessment of studies was geared toward the comparison of PC with IPAA vs. PC with ileostomy, not a univariate/prognostic framework to assess outcomes with PC with IPAA.
    - Based on quality assessment provided, there were likely no high-quality studies included (e.g., most were retrospective, response rates varied, inconsistent use of validated questionnaires)
  - **Imprecision:** Serious concern
    - Results not reported in sufficient detail to assess precision of results
  - **Indirectness:** No serious concern
    - Wang et al's results included people with UC and Crohn's disease and suggested some of the least favorable outcomes, but this is not considered to impact the overall statement for which certainty is being rated
  - **Inconsistency:** No serious concern
  - **Other considerations:** Reporting in Murphy 2015 is considered suboptimal (e.g., tabulated results required considerable validation or clarification from the full-text article and/or scale in consideration)

**PEYRIN-BIROULET 2016**

Peyrin-Biroulet L, Germain A, Patel AS, Lindsay JO. Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis. Aliment Pharmacol Ther. 2016 Oct;44(8):807-16. doi: 10.1111/apt.13763. Epub 2016 Aug 17. PubMed

Relevant to FAQ6

- **Study design:** systematic review of mostly observational studies
  - included one randomized, controlled trial
- **Population:** adults undergoing surgical treatment for UC
  - although specifies adults (≥18 years of age) as inclusion criterion, included some studies with people <18 years of age
- **Intervention:** surgical treatment for UC with total or subtotal colectomy, IPAA with J, S, or W pouch
  - Could include any of:
    - ileo-anal anastomosis or ileal pouch-anal anastomosis (IPAA)
    - restorative proctocolectomy
    - ileo-anal pouch procedure
    - subtotal or total colectomy
    - J pouch, S pouch, W pouch, or other pouch type
- **Comparison:** not applicable

- **Study inclusion criteria:**
  - studies reporting surgeries from 2002 onward (rationale being the timing of biologicals being introduced and more contemporary practice)
  - studies with ≥50 people

- **Number of studies:** 28
  - 26 full-text publications, 2 conference abstracts (quality assessment for abstracts not carried out)
  - 27 observational studies, 1 randomized, controlled trial
    - the randomized, controlled trial investigated how the method of antibiotic administration impacts surgical site infections
- **Number of participants:** 20,081
- **Duration of follow-up:** not reported, but outcomes reported as short-term (≤30 days postoperative) and long-term (>30 days)

- **Results and Certainty:** meta-analysis not performed due to "marked" clinical heterogeneity (not based on statistical heterogeneity)

**Short-term (≤30 days) and long-term (>30 days) risks after having colectomy for UC**

| Outcome | No. studies (no. people) | Range (no. events/sample size [%] for study with lowest and highest rate) | Certainty |
|---|---|---|---|
| Any infectious complication | 8 (1,134) | ≤30 days: 25/254 (10%) to 44/98 (45%) | Very low[1,2] |
| Pouchitis | 4 (946) | >30 days: 1/12 (8%) to 237/576 (41%) | Very low[1,2] |
| Pouch loss/failure/excision | 2 (239) | >30 days: 0%* to 2/12 (17%) | Very low [1,2] |
| Fistula | 1 (430) | ≤30 days: 0%* to 3/48 (6%)<br>>30 days: 0%* to 4/48 (8%) | Very low[1,2,3] |
| Small bowel obstruction | 6 (943) | ≤30 days: 1/61 (2%) to 8/68 (12%)<br>>30 days: 30/179 to 58/332 (both round to 17%) | ≤30 days: Very low[1,2†]<br>>30 days: Moderate[1] |
| Anastomotic leak | 3 (1,608) | ≤30 days: 1/199 (0.5%) to 5/52 (10%) | Very low[1,2‡] |
| Pelvic sepsis or pelvic abscess | 5 (1,941) | ≤30 days: 0/19, 0/27, and 0/199 (0%)* to 9/48 (19%) | Very low[1,2,4] |
| Ileus | 4 (458) | ≤30 days: 7/51 (14%) to 6/20 (30%)<br>>30 days: 3/106 (3%) to 17/68 (25%) | ≤30 days: Very low[1,2,4]<br>>30 days: Very low[1,2] |
| Fecal incontinence | 1 (179) | >30 days: 15/73 (21%) to 23/106 (22%) | Low[1,3] |
| Mortality | 11 (5,196) | ≤30 days: 0%* to 16/559 (3%) | Low[1,4] |

1, Serious concern for risk of bias because the mean, median, and mode of quality assessment scores for the studies was 10 (0 to 26 scale, with higher scores being better, based on the 28-item Downs and Black 1998 tool, with 2 items from the tool being considered not applicable for all rated studies). The 2 conference abstracts were not assessed for quality, and the authors assessed the single randomized, controlled trial based on the 2009 NICE Guidelines Manual, but these criteria are geared for comparative inference, which is an irrelevant concept here. Additionally, the authors only provide a summary table in an appendix based on the study, not based on the outcome assessed.

2, Very serious concern for imprecision. The authors did not meta-analyze their results due to "marked" clinical heterogeneity (rather than statistical heterogeneity). This clinical heterogeneity included things like the variety of procedures performed (not all studies were in people receiving PC with IPAA). We have attempted to capture this aspect of their systematic review via the domain of Indirectness where relevant given our interest is in people receiving PC with IPAA. However, the authors' decision not to meta-analyze results produces several ranges which are considerably broad, so we reflect the uncertainty this causes via the domain of Imprecision. In all instances where we were concerned with the imprecision of the results, we either had very serious concern with the imprecision of the range itself *or* we had serious concern with the imprecision of the range *plus* serious concern that at least one of the bounds of the range also suffered from serious imprecision (e.g., an estimate based on 2 events in 12 people). Accordingly, we assigned 2 downgrades.

3, Serious concern for inconsistency (due to only having one study reporting this outcome, thus precluding assessment of consistency of results)

4, Serious concern for indirectness (population informing estimate not sufficiently matched to population of interest for this evidence report, or concern over degree of match)

* Denominators were not reported for 0% risk estimates other than for pelvic sepsis or pelvic abscess. Three different cohorts had 0% risks for pelvic sepsis or pelvic abscess, so each is reported (0/19, 0/27, 0/199).

† Although the lower bound of the estimate for ≤30 days comes from a study in people having subtotal colectomy, the upper bound comes from a study that is sufficiently matched to the population of interest for this evidence report, and whether one says "about 2% to 17%" or "up to 17%" may have a small bowel obstruction within 30 days seems to offer sufficiently comparable inference such that we did not assign a downgrade for indirectness. Additionally, this estimate is Very low certainty regardless of its directness/indirectness.

‡ Although the lower bound of the estimate comes from a study in people receiving "colectomy" (without further detail), the upper bound comes from a study that is sufficiently matched to the population of interest for this evidence report, and whether one says "about 0.5% to 10%" or "up to 10%" may have an anastomotic leak within 30 days seems to offer sufficiently comparable inference such that we did not assign a downgrade for indirectness. Additionally, this estimate is Very low certainty regardless of its directness/indirectness.

**WHEAT 2016**

Wheat CL, Clark-Snustad K, Devine B, Grembowski D, Thornton TA, Ko CW. Worldwide Incidence of Colorectal Cancer, Leukemia, and Lymphoma in Inflammatory Bowel Disease: An Updated Systematic Review and Meta-Analysis. Gastroenterol Res Pract. 2016;2016:1632439. doi: 10.1155/2016/1632439. Epub 2016 May 16. PubMed

Although risk of colorectal cancer is the key outcome in FAQ 4, a full summary of this systematic review and meta-analysis was not prepared, because Castaño-Milla 2014 is specific to UC, whereas Wheat 2016 is not, and Castaño-Milla 2014 includes more studies than Wheat 2016. Although Wheat 2016 does provide results stratified by type of inflammatory bowel disease, it also only presents results for UC in a table (i.e., no meta-analysis was performed). Wheat 2016 made this decision based on heterogeneity that they considered to preclude pooling, but this appears to be based on statistical testing alone (e.g., $I^2$ estimates), which can be uninformative or misinformative when considering univariate estimates, especially with large datasets. Because of the later publication date of Wheat 2016, we wanted to ensure we would not miss any key publications subsequent to those aggregated by Castaño-Milla 2014. We checked all studies in Wheat 2016 that were published in 2013 or later that considered people with UC (either as the solitary group of interest or as a subgroup within the larger group of interest), and only study is not included in Castaño-Milla 2014: Selinger 2014. This referral center-based cohort study only had 504 people with UC and 24 instances of colorectal cancer over 8,006 person-years of follow-up, yielding an incidence rate estimate of 299.8 per 100,000 person-years (standard error 61.2, 95% CI 179.9 to 419.7). Accordingly, adding Selinger 2014 to the data in Castaño-Milla 2014 would likely have little effect (i.e., would likely yield results very comparable to those already presented by Castaño-Milla 2014). Therefore, this systematic review is not considered further in Parts 3 or 4.

## Characteristics of Select Sources Identified in Part 2 but not Advanced to Part 3

**AHMED ALI 2009**

Ahmed Ali 2009 is a Cochrane review summarizing trials comparing open vs. laparoscopically-assisted IPAA. Approximately 85% of the total included population had ulcerative colitis, and approximately 15% had familial adenomatous polyposis. Although this comparison is not of interest for this evidence report, one might conceivably be able to use this review as a source for univariate estimates (i.e., ignoring the open vs. laparoscopic concept and pooling the data from both groups to obtain univariate estimates of complications). However, it only reports things like “severe” complications, “procedure-specific complications”, and “minor complications”, which might be less meaningful than the individual outcomes in Peyrin-Biroulet 2016, which are a better match for scoped risks of interest. Ali 2009’s lumping of outcomes contributing to the aforementioned composite outcomes is also questionable. For instance, “minor” complications includes urinary tract infection (which is truly minor) and prolonged ileus and deep venous thrombosis (both of which are arguably much less minor than a urinary tract infection). Severe complications includes intra-abdominal abscess (which is clearly serious) and burst abdomen (which is arguably much more serious). Procedure-specific complications included various important outcomes, but people would likely value knowing the risks of these outcomes individually, rather than as a lumped group. Lastly, the Cochrane review is based on only 607 people vs. >20,000 people in Peyrin-Biroulet 2016; obviously quantity is not sufficient to achieve quality, but this still accentuates the above concerns and is worth noting.

**RAMAGE 2016**

Ramage 2016 is a systematic review of functional outcomes following PC with IPAA in older people who could have any reason for PC with IPAA (e.g., UC, Crohn’s, indeterminate colitis, collagenous colitis, familial adenomatous polyposis). Particularly given the availability of Heikens 2012 and Murphy 2015, Ramage 2016 was judged not to add meaningfully to this evidence report, so it was not progressed to Part 3 for critical appraisal.

# Evidence report for ulcerative colitis refractory to medication therapy

## Reference list

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**AHMED ALI 2009**
Ahmed Ali U, Keus F, Heikens JT, Bemelman WA, Berdah SV, Gooszen HG, van Laarhoven CJ. Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD006267. doi: 10.1002/14651858.CD006267.pub2. PubMed

**BREWER 2019**
Brewer MB. Ileal Pouch-Anal Anastomosis. Medscape. Last reviewed/updated October 4, 2019. Accessed October 18, 2019. Available at https://emedicine.medscape.com/article/1892231.

**CAMILLERI-BRENNAN 2003**
Camilleri-Brennan J, Munro A, Steele RJ. Does an ileoanal pouch offer a better quality of life than a permanent ileostomy for patients with ulcerative colitis? J Gastrointest Surg. 2003 Sep-Oct;7(6):814-9. PubMed

**CASTAÑO-MILLA 2014**
Castaño-Milla C, Chaparro M, Gisbert JP. Systematic review with meta-analysis: the declining risk of colorectal cancer in ulcerative colitis. Aliment Pharmacol Ther. 2014 Apr;39(7):645-59. PubMed

**CLEVELAND CLINIC 2014**
Cleveland Clinic. Ileal Pouches. Last reviewed/updated July 23, 2014. Accessed October 18, 2018. Available at https://my.clevelandclinic.org/health/articles/ileal-pouches.

**CORNISH 2007**
Cornish JA, Tan E, Teare J, Teoh TG, Rai R, Darzi AW, Paraskevas P, Clark SK, Tekkis PP. The effect of restorative proctocolectomy on sexual function, urinary function, fertility, pregnancy and delivery: a systematic review. Dis Colon Rectum. 2007 Aug;50(8):1128-38. Review. PubMed

**CROHN'S AND COLITIS FOUNDATION OF AMERICA ND**
Crohn's and Colitis Foundation of America. Surgery for Ulcerative Colitis. Date last reviewed/updated not provided. Accessed October 18, 2019. Available at https://www.crohnscolitisfoundation.org/what-is-ulcerative-colitis/surgery.

Crohn's and Colitis Foundation of America. Surgery for Crohn's Disease and Ulcerative Colitis. Date last reviewed/updated not provided. Accessed October 18, 2019. Available at https://www.crohnscolitisfoundation.org/sites/default/files/legacy/assets/pdfs/surgery_brochure_final.pdf.

**DYNAMED 2018**
DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T114507, Ulcerative Colitis in Adults; [updated 2018 Nov 30, cited 21 Oct 2019]. Available from https://www.dynamed.com/topics/dmp~AN~T114507.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T907551, Cyclosporine; [updated 2018 Nov 06, cited 21 Oct 2019]. Available from https://www.dynamed.com/topics/dmp~AN~T907551.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T908285, Tacrolimus; [updated 2018 Nov 06, cited 21 Oct 2019]. Available from https://www.dynamed.com/topics/dmp~AN~T908285.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T907851, Methotrexate; [updated 2018 Nov 30, cited 21 Oct 2019]. Available from https://www.dynamed.com/topics/dmp~AN~T907851.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T900402, Golimumab; [updated 2018 Nov 30, cited 21 Oct 2019]. Available from https://www.dynamed.com/topics/dmp~AN~T900402.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T908102, Vedolizumab; [updated 2018 Nov 30, cited 21 Oct 2019]. Available from https://www.dynamed.com/topics/dmp~AN~T908102.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T232895, Adalimumab; [updated 2018 Nov 30, cited place cited date here]. Available from https://www.dynamed.com/topics/dmp~AN~T232895.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T232803, Infliximab; [updated 2018 Nov 30, cited place cited date here]. Available from https://www.dynamed.com/topics/dmp~AN~T232803.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T361102, Systemic Corticosteroids for Asthma in Adults and Adolescents; [updated 2018 Nov 30, cited September 11, 2019]. Available from https://www.dynamed.com/topics/dmp~AN~T361102. Registration and login required.

DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T233279, Prednisone; [updated 2018 Nov 30, cited 2019 Oct 22. Available from https://www.dynamed.com/topics/dmp~AN~T233279.

**EUROQOL RESEARCH FOUNDATION 2018**
EuroQoL Research Foundation. EQ-5D-3L User Guide. 2018. Accessed October 15, 2019. Available at https://euroqol.org/publications/user-guides.

**GUYATT 1989**
Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, Tompkins C. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989 Mar;96(3):804-10. PubMed

**HEIKENS 2012**
Heikens JT, de Vries J, van Laarhoven CJ. Quality of life, health-related quality of life and health status in patients having restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis: a systematic review. Colorectal Dis. 2012 May;14(5):536-44. doi: 10.1111/j.1463-1318.2010.02538.x. PubMed

**IRVINE 1996**
Irvine EJ, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. Am J Gastroenterol. 1996 Aug;91(8):1571-8. PubMed

**KUCHARZIK 2019**
Kucharzik T, Dignass AU, Atreya R, Bokemeyer B, Esters P, Herrlinger K, Kannengießer K, Kienle P, Langhorst J, Lügering A, Schreiber S, Stallmach A, Stein J, Sturm A, Teich N, Siegmund B, Andus T, Autschbach F, Bachmann O, Baretton G, Baumgart DC, Bettenworth D, Bläker M, Buderus S, Büning J, Ehehalt R, Fellermann K, Fichtner-Feigl S, Götz M, Gross C, Hartmann F, Hartmann P, In der Smitten S, Häuser W, Helwig U, Kaltz B, Kanbach I, Keller KM, Klaus J, Koletzko S, Kroesen A, Kruis W, Kühbacher T, Leifeld L, Maaser C, Matthes H, Moog G, Ockenga J, Pace A, Reinshagen M, Rijcken E, Rogler G, Stange E, Veltkamp C, Zemke J. Updated S3-Guideline Ulcerative Colitis. German Society for Digestive and Metabolic Diseases (DGVS). Z Gastroenterol. 2019 Feb;57(2):162-241. doi: 10.1055/a-0824-0861. Epub 2019 Jan 17. PubMed

**KURUVILLA 2012**
Kuruvilla K, Osler T, Hyman NH. A comparison of the quality of life of ulcerative colitis patients after IPAA vs ileostomy. Dis Colon Rectum. 2012 Nov;55(11):1131-7. doi: 10.1097/DCR.0b013e3182690870. PubMed

**LEE 2019**
Lee S, Crowe M, Seow CH, Kotze PG, Kaplan GG, Metcalfe A, Ricciuto A, Benchimol EI, Kuenzig ME. The impact of surgical therapies for inflammatory bowel disease on female fertility. Cochrane Database Syst Rev. 2019 Jul 23;7:CD012711. doi: 10.1002/14651858.CD012711.pub2. PubMed

**LUTGENS 2013**
Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis. 2013 Mar-Apr;19(4):789-99. doi: 10.1097/MIB.0b013e31828029c0. PubMed

**MAHMOUD 2018**
Mahmoud NN, Aarons CB, Bleier JIS, Saur NM, Shanmugan S. Total Proctocolectomy with J-pouch Reconstruction for Ulcerative Colitis. Last reviewed/updated February 27, 2018. Accessed October 18, 2018. Available at https://www.pennmedicine.org/for-health-care-professionals/for-physicians/physician-education-and-resources/clinical-briefings/2018/february/total-proctocolectomy-with-jpouch-reconstruction-for-ulcerative-colitis.

**MAYO CLINIC 2019**
Mayo Clinic. Ileoanal anastomosis (J-pouch) surgery. Last updated/reviewed March 23, 2019. Accessed October 18, 2019. Available at https://www.mayoclinic.org/tests-procedures/j-pouch-surgery/about/pac-20385069 .

**MOWSCHENSON 2000**
Mowschenson PM, Critchlow JF, Peppercorn MA. Ileoanal pouch operation: long-term outcome with or without diverting ileostomy. Arch Surg. 2000 Apr;135(4):463-5; discussion 465-6. PubMed

**MURPHY 2015**
Murphy PB, Khot Z, Vogt KN, Ott M, Dubois L. Quality of Life After Total Proctocolectomy With Ileostomy or IPAA: A Systematic Review. Dis Colon Rectum. 2015 Sep;58(9):899-908. doi: 10.1097/DCR.0000000000000418. PubMed

**NIH 2019**
National Institutes of Health, U.S. National Library of Medicine. Total proctocolectomy and ileal-anal pouch. Last reviewed/updated September 3, 2018. Accessed October 18, 2019. Available at https://medlineplus.gov/ency/article/007380.htm.

**NORDIN 2002**
Nordin K, Påhlman L, Larsson K, Sundberg-Hjelm M, Lööf L. Health-related quality of life and psychological distress in a population-based sample of Swedish patients with inflammatory bowel disease. Scand J Gastroenterol. 2002 Apr;37(4):450-7. PubMed

**PEYRIN-BIROULET 2016**
Peyrin-Biroulet L, Germain A, Patel AS, Lindsay JO. Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis. Aliment Pharmacol Ther. 2016 Oct;44(8):807-16. doi: 10.1111/apt.13763. Epub 2016 Aug 17. PubMed

**RAJARATNAM 2011**
Rajaratnam SG, Eglinton TW, Hider P, Fearnhead NS. Impact of ileal pouch-anal anastomosis on female fertility: meta-analysis and systematic review. Int J Colorectal Dis. 2011 Nov;26(11):1365-74. doi: 10.1007/s00384-011-1274-9. Epub 2011 Jul 16. PubMed

**RAMAGE 2016**
Ramage L, Qiu S, Georgiou P, Tekkis P, Tan E. Functional outcomes following ileal pouch-anal anastomosis (IPAA) in older patients: a systematic review. Int J Colorectal Dis. 2016 Mar;31(3):481-92. doi: 10.1007/s00384-015-2475-4. Epub 2016 Jan 12. PubMed

**RUBIN 2019**
Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384-413. doi: 10.14309/ajg.0000000000000152. PubMed

**SELVAGGI 2014**
Selvaggi F, Pellino G, Canonico S, Sciaudone G. Systematic review of cuff and pouch cancer in patients with ileal pelvic pouch for ulcerative colitis. Inflamm Bowel Dis. 2014 Jul;20(7):1296-308. doi: 10.1097/MIB.0000000000000026. PubMed

**UCSF HEALTH ND**
University of California San Francisco. Special Concerns for People with J-Pouches. Date last reviewed/updated not provided. Accessed October 21, 2019. Available at https://www.ucsfhealth.org/education/special_concerns_for_people_with_j-pouches/.

**VAN DER VALK 2012**
van der Valk ME, Mangen M-JJ, Dijkstra G, et al. Is there a difference in quality of life and costs between ulcerative colitis patients with a pouch or an ileostomy? Gastroenterology. 2012;142:S263.

**VATHER 2013**
Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. J Gastrointest Surg. 2013 May;17(5):962-72. doi: 10.1007/s11605-013-2148-y. Epub 2013 Feb 2. Review. PubMed

**WALJEE 2006**
Waljee A, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. Gut. 2006 Nov;55(11):1575-80. Epub 2006 Jun 13. PubMed

**WESTON-PETRIDES 2008**
Weston-Petrides GK, Lovegrove RE, Tilney HS, Heriot AG, Nicholls RJ, Mortensen NJ, Fazio VW, Tekkis PP. Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy. Arch Surg. 2008 Apr;143(4):406-12. doi: 10.1001/archsurg.143.4.406. Review. PubMed

**WHEAT 2016**
Wheat CL, Clark-Snustad K, Devine B, Grembowski D, Thornton TA, Ko CW. Worldwide Incidence of Colorectal Cancer, Leukemia, and Lymphoma in Inflammatory Bowel Disease: An Updated Systematic Review and Meta-Analysis. Gastroenterol Res Pract. 2016;2016:1632439. doi: 10.1155/2016/1632439. Epub 2016 May 16. PubMed