

Supplementary Data File 1

Systematic Literature Review: Search Algorithm

Database: PubMed

Date: [INSERT]

Search Terms:

Crohn's[Title/Abstract] AND fistul[Title/Abstract] AND (epidemiolog*[Title/Abstract] OR incidence[Title/Abstract] OR prevalence[Title/Abstract]) AND (US[Title/Abstract] OR U.S.[Title/Abstract] OR USA[Title/Abstract] OR U.S.A.[Title/Abstract] OR "United States"[Title/Abstract] OR America*[Title/Abstract] OR "state of"[Title/Abstract] OR county[Title/Abstract]) AND ("1970/01/01"[Date - Publication] : "2017/02/15"[Date - Publication])*

Supplementary Data Content 2

Estimation of Duration of Fistulizing Crohn' Disease (CD)

Fistulizing CD is a chronic condition that can relapse in a fraction of patients. Therefore, the estimated duration of fistulizing CD is not simply based on the duration of a single fistula episode, but also on the number of fistula episodes suffered, and on the duration of the periods of time between different episodes. As discussed in the manuscript, this is a conservative approach (i.e. leading to higher patient numbers).

Separate calculations have been conducted for estimating the duration of fistulizing CD for each type of fistula (i.e. anal, rectovaginal, enterocutaneous, and internal). The methodology of the calculation is explained below.

Step 1: Duration of Fistulizing CD

The authors estimated the duration of the fistulizing disease for each type of fistula as follows:

- Duration of fistula in patients with 1 episode:
 - Duration of 1 fistula episode
- Duration of fistula in patients with 2 episodes:
 - Duration of 2 fistula episodes + duration of 1 interval between fistula episodes
- Duration of fistula in patients with 3 episodes:
 - Duration of 3 fistula episodes + duration of 2 intervals between fistula episodes
- Duration of fistula in patients with 4 episodes:
 - Duration of 4 fistula episodes + duration of 3 intervals between fistula episodes
- Duration of fistula in patients with 5 episodes:
 - Duration of 5 fistula episodes + duration of 4 intervals between fistula episodes

The data sources used for conducting the calculations described above were the papers by Bell et al. 2003 and Schwartz et al. 2002.

The paper by Bell et al. 2003 was selected as it is the only study that has analyzed in detail and in a reliable manner the duration of fistula episodes in CD (Table 1).

TABLE 1. Duration of Fistula Episode

Type of fistula	Duration of fistula episode ^a (median)
Anal	3.6 years ^b
Rectovaginal	2.2 years
Enterocutaneous	0.5 years
Internal	0.8 years

^aReported by Bell et al., 2003 in months, have been translated to years.

^bDuration of anal fistulas is reported by Bell et al. 2003 separately for complex and simple fistula (3.6 and 3.7 years, respectively). We calculated the overall duration of an episode of anal fistulas as the weighted average of the duration of one episode of simple and one episode of complex fistula, considering that, according to literature, in average 75% of anal fistulas in CD are complex (Eglinton et al. 2012; Molendijk et al. 2014).

On the other hand, Schwartz et al. 2002 was used as the source for the median time between fistulizing episodes, which was 2.8 years. In this way, for each type of fistula, and based on the number of episodes suffered, we estimated the duration of fistulizing CD (Table 2).

TABLE 2. Duration of Fistulizing CD Based on the Number of Fistula Episodes Suffered.

Anal	
Number of episodes	Duration of fistulizing CD disease (median)
1	3.6 years
2	10.0 years
3	12.8 years
4	22.8 years
5	29.2 years
Rectovaginal	
Number of episodes	Duration of fistulizing CD disease (median)
1	2.2 years
2	7.1 years
3	12.1 years
4	17.1 years
5	22.0 years

Enterocutaneous	
Number of episodes	Duration of fistulizing CD disease (median)
1	0.5 years
2	3.9 years
3	7.2 years
4	10.5 years
5	13.8 years
Internal	
Number of episodes	Duration of fistulizing CD disease (median)
1	0.8 years
2	4.4 years
3	8.0 years
4	11.5 years
5	15.1 years

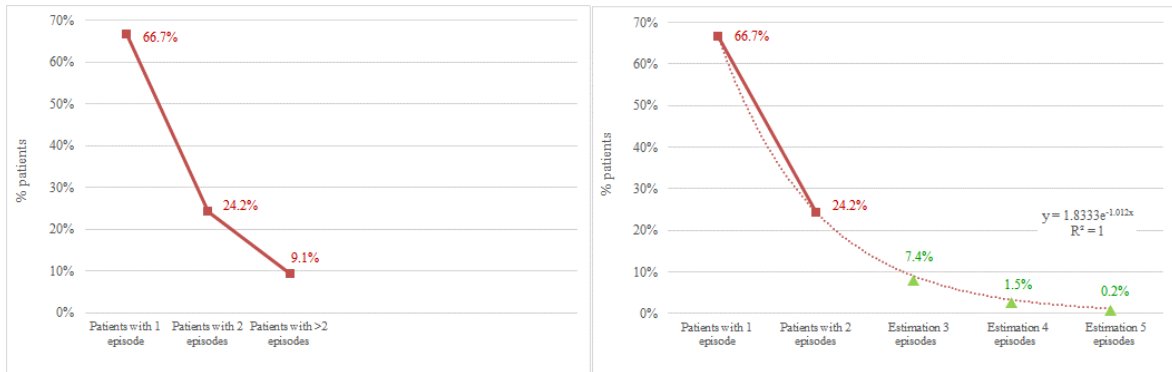
Step 2: Number of fistula episodes suffered

The considered number of fistula episodes suffered by CD patients is based on the data reported by Schwartz et al. 2002. In the case of anal fistulas they reported the proportions of patients with 1, 2, or >2 episodes (66.7%, 24.2%, and 9.1% respectively).

Concerning the proportion of patients with >2 episodes, we have made an estimation about how this 9.1% of patients is split in patients with different number of episodes. This is more realistic than simply assuming that >2 episodes means 3 episodes. That estimate is based on the fact the authors have found, by means of logistic regression, that the reported proportion of patients with 1, 2, or >2 episodes follows an exponential trend ($r^2=1$). Therefore, we estimated the percentages of patients with 3, 4, 5... episodes, as those percentages that, having a sum of 9.1%, are able follow as much as possible an exponential trend.

This is illustrated for anal fistulas in Figure 1.

FIGURE 1. Anal Fistulas: Estimation of the Proportion of Patients with 1, 2, 3... Fistula Episodes, From the Reported Proportion of Patients with >2 Fistula Episodes (9.1%) (Schwartz et al. 2002)



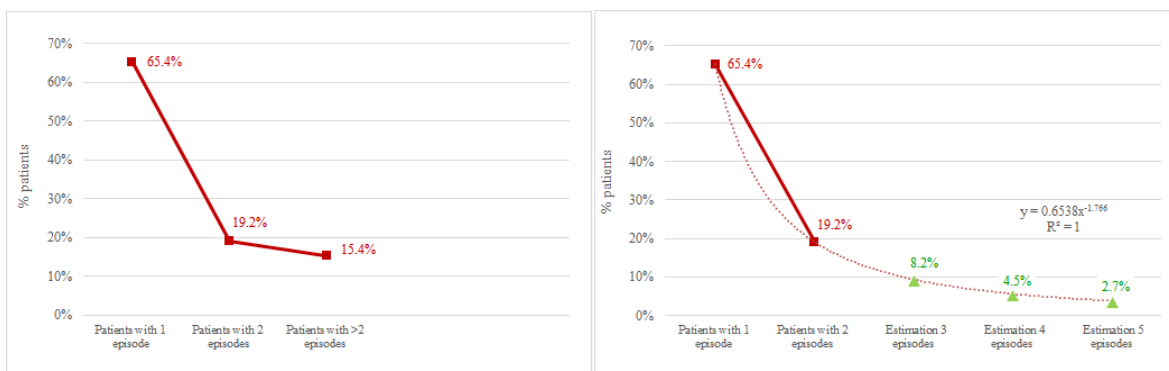
Proportions of patients with 1, 2 or > 2 episodes, as reported by Schwartz et al. 2002

Estimated split of proportions of patients with >2 episodes (green color)

In the case of fistulas other than anal (i.e. rectovaginal, enterocutaneous, and internal), the proportions of patients with 1, 2, or >2 episodes can be inferred from data reported by Schwartz et al. 2002. This is because they also reported the proportions of patients with 1, 2, or >2 episodes in the population of CD patients with any type of fistula. Therefore, it was possible to calculate by subtraction the proportions of patients with 1, 2, or >2 episodes in the group of patients with fistulas other than anal. These proportions are 65.4%, 19.2%, and 15.4% respectively. We applied such proportions to all patients with fistulas other than anal (i.e. with rectovaginal, enterocutaneous, or internal fistulas), as Schwartz et al., 2002 did not provide data that allowed estimating such proportions for each of these specific types of fistulas.

Concerning the proportion of patients with >2 episodes (15.4%), an approach analogous to that shown above for anal fistulas has allowed us to estimate how this 15.4% is split between patients with 3, 4, 5... episodes (Figure 2).

FIGURE 2. Fistulas Other Than Anal: Estimation of the Proportion of Patients 3, 4, 5... Fistula Episodes, From the Reported Proportion of Patients With >2 Fistula Episodes (15.4%) (Schwartz et al. 2002).



Proportions of patients with 1, 2 or > 2 episodes, as reported by Schwartz et al. 2002.

Estimated split of proportions of patients with >2 episodes (green color).

Step 3: Overall duration of fistulizing CD

Last, for each type of fistula, the overall duration of fistulizing CD has been estimated as the weighted average of the duration of fistulizing CD in patients suffering different numbers of episodes.

This is illustrated in Table 3.

TABLE 3. Calculation of Overall Duration of Fistulizing Per Type of Fistula.

Anal			
Number of episodes	Percentage of patients^a	Duration of fistulizing CD (median)^b	Duration of fistulizing CD (weighted average of medians)
Patients with 1 episode	66.7%	3.6 years	6.2 years
Patients with 2 episodes	24.2%	10.0 years	
Patients with 3 episodes	7.4%	12.8 years	
Patients with 4 episodes	1.5%	22.8 years	
Patients with 5 episodes	0.2%	29.2 years	
Rectovaginal			
Number of episodes	Percentage of patients^c	Duration of fistulizing CD (median)^b	Duration of fistulizing CD (weighted average of medians)
Patients with 1 episode	65.4%	2.2 years	5.1 years
Patients with 2 episodes	19.2%	7.1 years	
Patients with 3 episodes	8.2%	12.1 years	
Patients with 4 episodes	4.5%	17.1 years	
Patients with 5 episodes	2.7%	22.0 years	
Enterocutaneous			
Number of episodes	Percentage of patients^c	Duration of fistulizing CD (median)^b	Duration of fistulizing CD (weighted average of medians)
Patients with 1 episode	65.4%	0.5 years	2.5 years
Patients with 2 episodes	19.2%	3.9 years	
Patients with 3 episodes	8.2%	7.2 years	
Patients with 4 episodes	4.5%	10.5 years	
Patients with 5 episodes	2.7%	13.8 years	
Internal			
Number of episodes	Percentage of patients^c	Duration of fistulizing CD (median)^b	Duration of fistulizing CD (weighted average of medians)
Patients with 1 episode	65.4%	0.8 years	2.9 years
Patients with 2 episodes	19.2%	4.4 years	
Patients with 3 episodes	8.2%	8.0 years	
Patients with 4 episodes	4.5%	11.5 years	
Patients with 5 episodes	2.7%	15.1 years	

^aFrom Figure 1 (Step 2).

^bFrom Table 2 (Step 1).

^cFrom Figure 2 (Step 2).

In summary, following this calculation strategy, the resulting durations of fistulizing CD were **6.2 years** for perianal fistulizing disease, **5.1 years** for rectovaginal fistulizing disease, **2.5 years** for enterocutaneous fistulizing disease, and **2.9 years** for internal fistulizing disease. These results support the chronic nature of fistulas in CD patients.

For the estimation of fistula duration, no confidence intervals could be derived, as they were not reported in the papers used as data sources.

Supplementary Data Content 3

Population-Based Database Analysis: Included Diagnosis and Procedure Codes

A. Diagnosis Codes

Anal Fistula

Code	Description
565.1	Anal Fistula

Rectovaginal Fistula

Code	Description
619.1	Digestive-genital tract fistula female

Enterocutaneous Fistula

Code	Description
569.81	Fistula of intestine, excluding rectum and anus

Adjustment factors applied to the patient counts used in the analysis:

Code 569.81: Total number of identified records multiplied by 19% based on the reported proportion of intestinal non-perianal fistulas that are enterocutaneous (Schwartz et al. 2002).

Internal Fistula

Code	Description
569.81	Fistula of intestine; excluding rectum and anus*
593.82	Ureteral fistula
599.1	Urethral fistula
530.84	Tracheoesophageal fistula
537.4	Fistula of stomach or duodenum
576.4	Fistula of bile duct
596.1	Intestinovesical fistula
575.5	Fistula of gallbladder

Adjustment factors applied to the patient counts used in the analysis:

Code 569.81: Total number of identified records multiplied by 81% based on the assignment of 19% of fistulas under this group to enterocutaneous fistula (Schwartz et al. 2002).

B. Procedure Codes

Anal Fistula

Code	Description
46258	Placement of seton
46280	Transsphincteric, suprasphincteric, extrasphincteric or multiple, including placement of seton, when performed
49.12	Anal fistulectomy
46275	Surgical treatment of anal fistula (fistulectomy/fistulotomy); intersphincteric. (LIFT covered under code)
49.11	Anal fistulotomy
46706	Repair of anal fistula with fibrin glue
46707	Repair of anorectal fistula with plug
46288	Closure of anal fistula with rectal advancement flap
49.73	Closure of anal fistula
46020	Placement of seton
46030	Removal of anal seton; other marker
46270	Surgical treatment of anal fistula (fistulectomy/fistulotomy); subcutaneous
46285	Surgical treatment of anal fistula (fistulectomy/fistulotomy); second stage
46715	Repair of low imperforate anus; with anoperineal fistula (cut-back procedure)
48.93	Repair of perirectal fistula
46060	Incision and drainage of ischiorectal or intramural abscess with fistulectomy or fistulotomy submuscular with or without placement of seton.
49.01	Incision of perianal abscess
45000	Transrectal drainage of pelvic abscess
45005	Incision and drainage of submucosal abscess rectum
45020	Incision and drainage of deep supralelevator pelvirectal or retrorectal abscess
46040	Incision and drainage of ischiorectal and/or perirectal abscess (separate procedure)
46045	Incision and drainage of intramural intramuscular or submucosal abscess transanal under anesthesia
46050	Incision and drainage perianal abscess superficial
45562	Exploration; repair; and presacral drainage for rectal injury;
45563	Exploration; repair; and presacral drainage for rectal injury; with colostomy
46.10	Colostomy, not otherwise specified
46.11	Temporary colostomy
46.13	Permanent colostomy
46.14	Delayed opening of colostomy
46.20	Ileostomy, not otherwise specified
46.21	Temporary ileostomy
46.22	Continent ileostomy
46.23	Other permanent ileostomy
46.24	Delayed opening of ileostomy
46.31	Delayed opening of other enterostomy
46.39	Other enterostomy
44143	Partial Colectomy, Colostomy (Hartmann)
44310	Creation Enterostomy (Jejunostomy or Ileostomy)
44320	Creation Colostomy
45112	Proctectomy, combined abdominoperineal, pull-through procedure (eg, colo-anal anastomosis)
45113	Proctectomy, partial, with rectal mucosectomy, ileoanal anastomosis, creation of ileal reservoir (S or J), with or without loop ileostomy
45119	Proctectomy, combined abdominoperineal pull-through procedure (eg, colo-anal anastomosis), with creation of colonic reservoir (eg, J-pouch), with diverting enterostomy when performed
45123	Proctectomy, partial, without anastomosis, perineal approach

Adjustment factors applied to the patient counts used in the analysis:

Anorectal drainage-related codes (49.01 to 45563): 50% (50% anal/rectal abscesses are fistula-related; Cologne et al. 2014. Clinical assessment and imaging modalities of fistula in ano. In: Anal fistula, chapter 6 pp 31-37. Ed. Abcarian H. Springer 2014).

Stoma-related codes (4610 to 44320): 50% (50% of ostomies in Crohn's disease are related to anal fistula; Martí-Gallostra et al. The role of a defunctioning stoma for colonic and perianal Crohn's disease in the biological era. Scand J Gastroenterology. 2017;52;251–256).

Proctectomy-related codes (45112 to 45123): 78% (78% of proctectomies in Crohn's disease are related to anal fistula; Figg et al. Perineal Crohn's Disease: an indicator of poor prognosis and potential proctectomy. Dis Colon Rectum. 2009; 52:646-650)

Rectovaginal Fistula

Code	Description
46740	Repair of high imperforate anus with rectourethral or rectovaginal fistula; perineal or sacroperineal approach
46742	Repair of high imperforate anus with rectourethral or rectovaginal fistula; combined transabdominal and sacroperineal approaches
57300	Closure of rectovaginal fistula; vaginal or transanal approach
57305	Closure of rectovaginal fistula; vaginal or transanal approach
57307	Closure of rectovaginal fistula; abdominal approach, with concomitant colostomy
57308	Closure of rectovaginal fistula; transperineal approach, with perineal body reconstruction, with or without levator plication
70.73	Repair of rectovaginal fistula
70.74	Repair of other vaginoenteric fistula

Enterocutaneous Fistula

No specific surgical codes available for this condition.

Internal Fistula

Code	Description
29.53	Closure of other fistula of pharynx
58.43	Closure of other fistula of urethra
42.84	Repair of esophageal fistula not elsewhere classified
44.63	Closure of other gastric fistula
46.72	Closure of fistula of duodenum
46.74	Closure of fistula of small intestine, except duodenum
47.92	Closure of appendiceal fistula
51.93	Closure of other biliary fistula
57.83	Closure of fistula involving bladder and intestine
70.72	Repair of colovaginal fistula
43880	Closure of gastrocolic fistula
44650	Closure of enteroenteric or enterocolic fistula
44660	Closure of enterovesical fistula; without intestinal or bladder resection
44661	Closure of enterovesical fistula; with intestine and/or bladder resection
46.76	Closure of fistula of large intestine

Supplementary Data Content 4

Systematic Literature Review: Excluded Articles and Reasons for Exclusion

Article	Main Reason(s) for Exclusion
Schwartz et al. 2001[a]	<ul style="list-style-type: none"> • Population: reported data correspond to studies conducted in referral centers; studied patients belonged to specific subgroups (e.g. patients with Crohn's disease of the colon)* • Geography: reported rates do not correspond to US studies (Germany and UK)* • Outcomes: results do not refer to specifically to fistulas as they include other perianal complications, such as abscesses or fissures; data presented cumulatively along disease course*/**
Greenstein et al. 1974 [b]	<ul style="list-style-type: none"> • Population: study conducted in referral center; only patients with colonic Crohn's disease included (predefined selection criteria) • Outcomes: results presented cumulatively along disease course**
Farmer et at. 1975 [c]	<ul style="list-style-type: none"> • Population: study conducted in referral center • Outcomes: results presented cumulatively along disease course**
Homan et al. 1976 [d]	<ul style="list-style-type: none"> • Population: study conducted in referral center • Outcomes: results presented cumulatively along disease course**
Rankin et al. 1979 [e]	<ul style="list-style-type: none"> • Population: study conducted in referral centers • Type of study: clinical trial (i.e. patients included according to predefined selection criteria) • Outcomes: results presented cumulatively along disease course**
Williams et al. 1981 [f]	<ul style="list-style-type: none"> • Population: study conducted in referral center • Outcomes: results presented cumulatively along disease course**

*Hobbiss JH, Schoefield PF. Management of perianal Crohn's disease. *J Roy Soc Med.* 1982; 75:414–417.

Goebell H. Perianal complications of Crohn's disease. *Neth J Med.* 1990;37(Suppl.) 1:S47–S51.

**Unsuitable to derive incidence or prevalence.

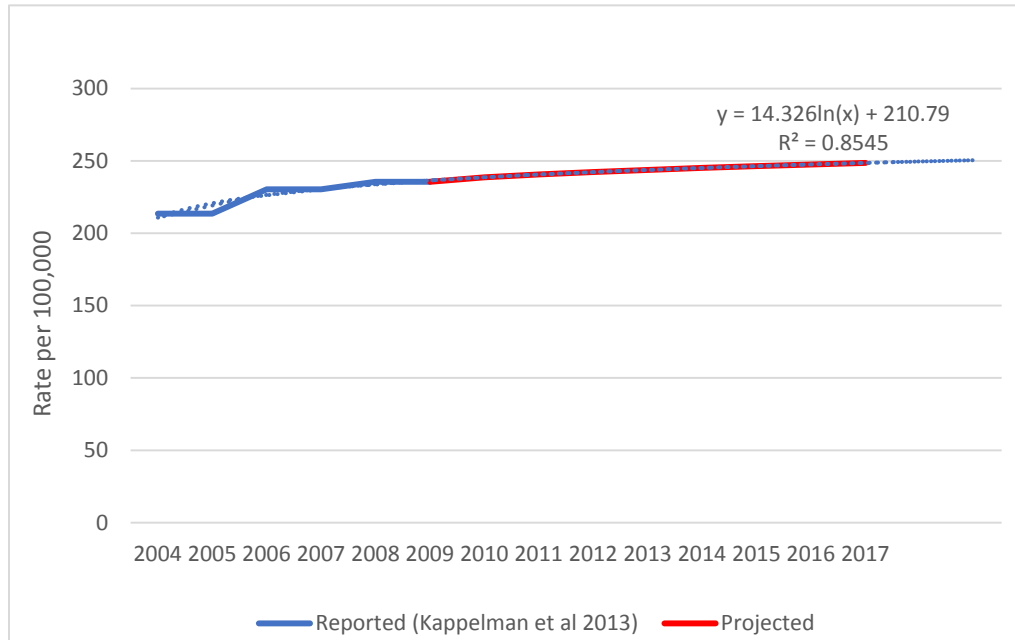
References

- a. Schwartz DA, Pemberton JH, Sandborn WJ. Diagnosis and treatment of perianal fistulas in Crohn disease. *Ann Intern Med.* 2001;135:906–918.
- b. Greenstein AJ, Kark AE, Dreiling DA. Crohn's disease of the colon. I. Fistula in Crohn's disease of the colon, classification presenting features and management in 63 patients. *Am J Gastroenterol.* 1974;62:419–429.
- c. Farmer RG, Hawk WA, Turnbull RB, Jr. Clinical patterns in Crohn's disease: a statistical study of 615 cases. *Gastroenterology.* 1975;68:627–635.
- d. Homan WP, Tang C, Thorbjarnarson B. Anal lesions complicating Crohn disease. *Arc Surg.* 1976;111:1333–1335.
- e. Rankin GB, Watts HD, Melnyk CS, et al. National Cooperative Crohn's Disease Study: extraintestinal manifestations and perianal complications. *Gastroenterology.* 1979;77:914–920.
- f. Williams DR, Collier JA, Corman ML, et al. Anal complications in Crohn's disease. *Dis Colon Rectum.* 1981;24:22–24.

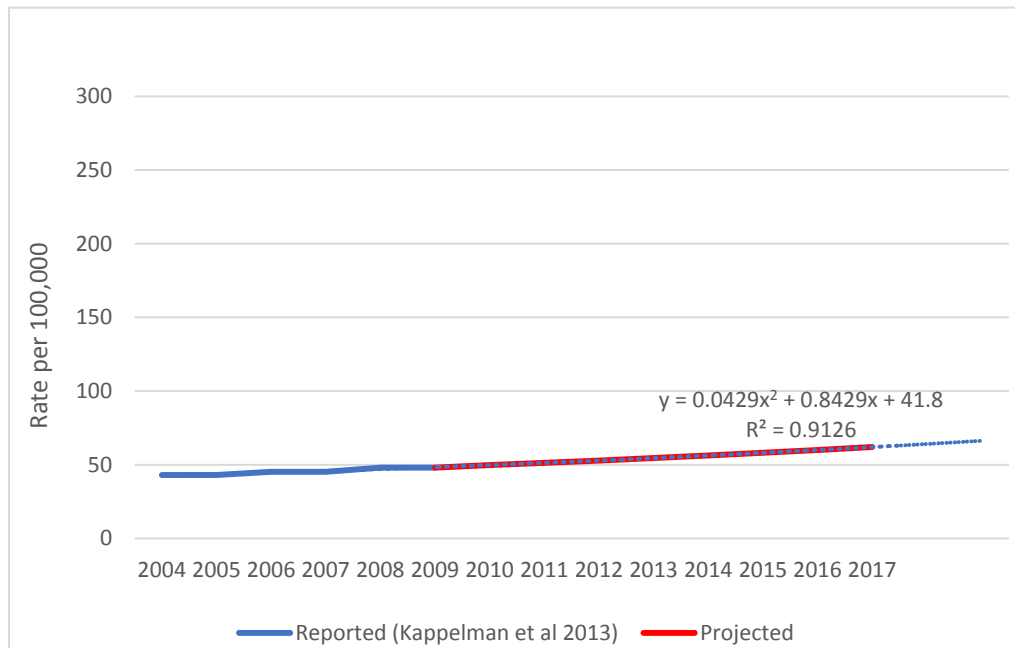
Supplementary Data Content 5

Projected Prevalence of Crohn's Disease in US to 2017

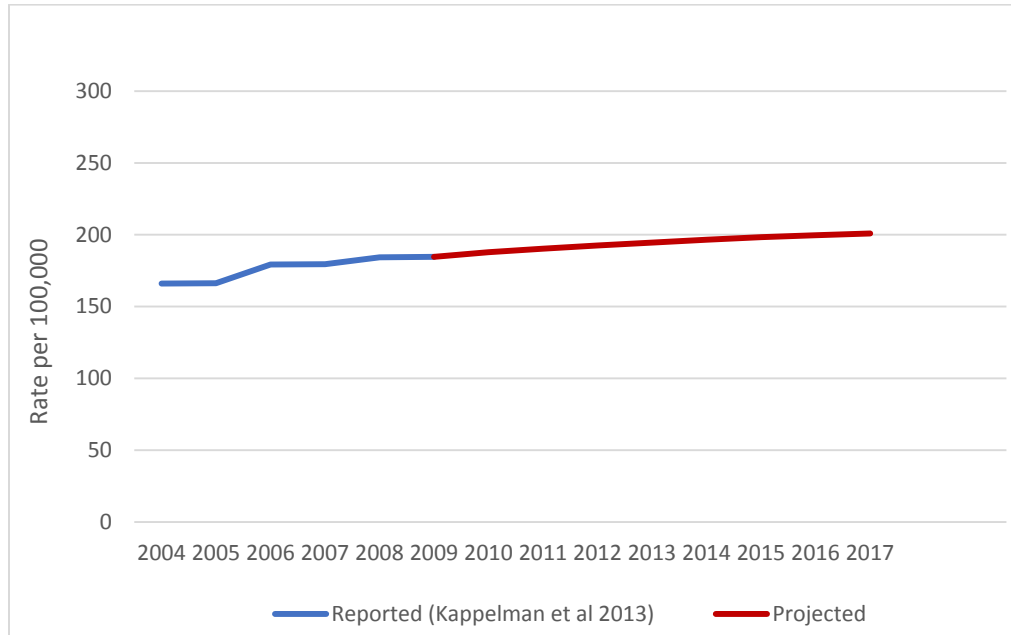
A. Adult population (≥ 20 years)



B. Pediatric population (< 20 years)



C. Overall population



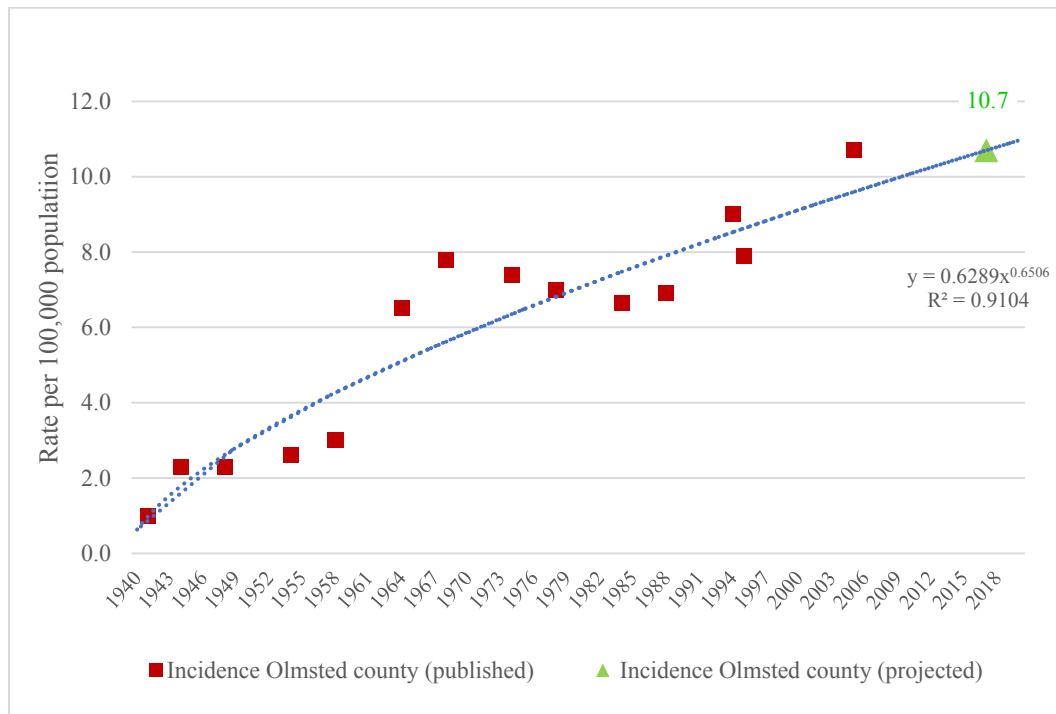
Projection of US Crohn's disease prevalence reported by Kappelman et al. [16] to 2017. It has been conservatively assumed that the rising trend of Crohn's disease prevalence reported by Kappelman et al. [16] has continued till present. Projection is based on logistic regression (least squares method) using the best adjustment found.

Projections were conducted separately for adult (A) and pediatric (B) populations, and then both were consolidated (C) considering age distribution in the US population.

Supplementary Content File 6

Projected Incidence and Prevalence of Crohn's Disease in Olmsted County, Minnesota, to 2017

A. Incidence of Crohn's disease in Olmsted County



For projection purposes, incidence rates reported for a given time interval have been assigned to the midpoint corresponding to such an interval. In cases where more than one rate is obtained for a single year, the mean has been selected. Projection is based on logistic regression (least squares method) using the best adjustment found.

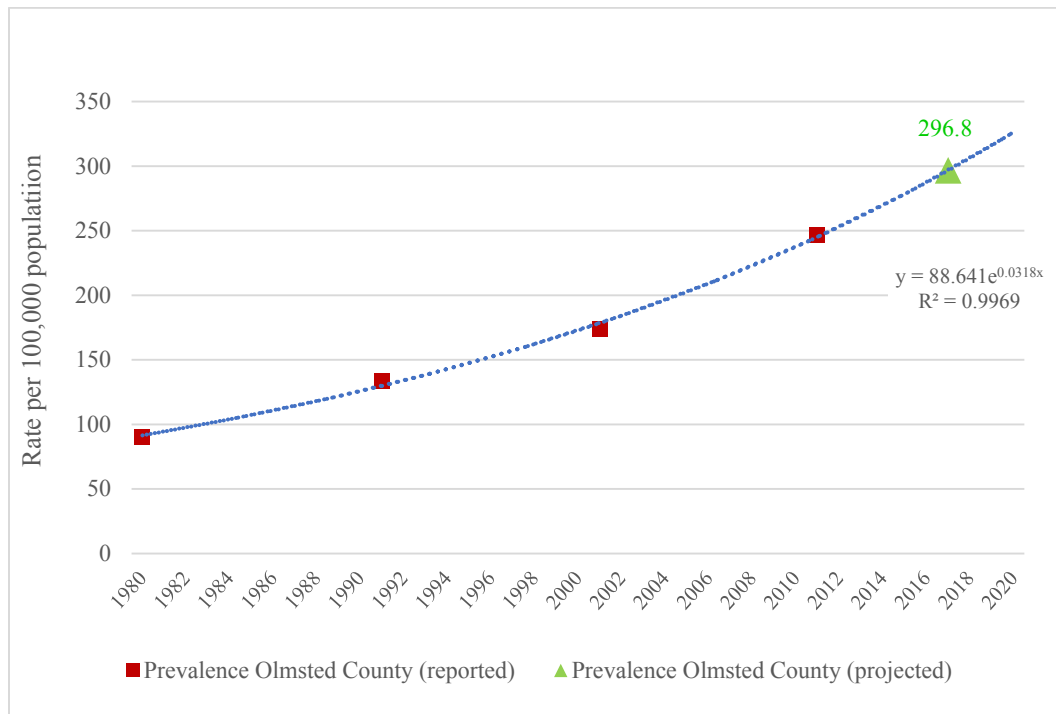
Sources for incidence rates corresponding to Olmsted County:

Loftus EV, Jr., et al. *Gastroenterology*. 1998;114:1161–68. [14]

Loftus CG, et al. *Inflamm Bowel Dis*. 2007;13:254–261. [15]

Shivashankar R, et al. *Clin Gastroenterol Hepatol*. 2017;15: 857–863. [11]

B. Prevalence of Crohn's disease in Olmsted County



Projection is based on mean logistic regression (least squares method) using the best adjustment found.

Sources for incidence rates corresponding to Olmsted County:

Gollop JH, et al. *Gut*. 1988;29:49–56. [17]

Loftus EV, Jr., et al. *Gastroenterology*. 1998;114:1161–1168. [14]

Loftus CG, et al. *Inflamm Bowel Dis*. 2007;13:254–261. [15]

Shivashankar R, et al. *Clin Gastroenterol Hepatol*. 2017;15: 857–863. [11]