The 100 Most-Cited Articles in the Field of Colorectal Diseases from 1955 to 2020: A Bibliometric Analysis

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ABSTRACT

Background: *The number of times that an article is cited could reflect its impact. This study aims to recognize and analyze the characteristics of the most frequently cited articles in the field of colorectal diseases.*

Methods: *We identified the 100 most-cited articles using the terms "colorectal," "colon," "rectal," "IBD," "ulcerative colitis," "Crohn's disease," or "colonoscopy" in Web of Science. The articles were analyzed to evaluate the characteristics, including the number of citations, country of origin, the institution of origin based on the first author's affiliation, study type, and others.*

Results: *Of the top-cited publications, the number of citations ranged from 1575 to 9283, with a mean of 2504.11 citations. The journal with the greatest number of most-cited articles was the New England Journal of Medicine (n = 23), followed by Science (n = 14) and Nature (n = 12). These papers were published in 14 different countries, of which more than half were from the United States (n = 60). The most popular field was colorectal cancer (n = 45), followed by colon tumors (n = 21). Most of the papers were basic science studies (n = 43) and randomized controlled trials (n = 30). Regarding the level of evidence, there were 5 studies at level I, 29 at level II, and 5, 1, and 15 studies at levels III, IV, and V, respectively.*

Conclusion: *Our study could provide a historical perspective on scientific progress in the field of colorectal diseases. These 100 most-cited articles are of great significance for helping researchers understand this field over time.*

Keywords: *Bibliometrics, citation analysis, colorectal diseases*

INTRODUCTION

The speed of updating knowledge is likely to increase as the internet becomes more accessible. Researchers could be overwhelmed by the amount of information and could find directions of interest for research difficult. Thus, there is an urgent need to explore ways that help researchers effectively access useful articles in their research fields.

In academia, the number of citations that an article receives does not necessarily mean it is the most influential. However, it could reflect how celebrated that article has been in its branch of learning, with the implication being that the more the number of times it is cited, the greater the paper's worth. Although the value of citation counts has been debated, a high citation count is a direct proxy for a paper's acceptance in its scientific field. Utilizing mathematical and statistical methods, bibliometric citation analysis can quickly filter out a large number of useful articles.[1]

A classic citation is currently defined as a top-cited publication, as identified from the Science Citation Index or Social Sciences Citation Index.[2] At present, citation analysis has been widely used in various specialties, including gastric diseases, hepatology, urology,[3-5] and others. To date, there is no comprehensive list of classic citations within the specialty of colorectal diseases. Therefore, the purpose of our study was to identify and evaluate the characteristics of top-cited publications concerning colorectal diseases and to try to gain insights into this area. The widely used databases for citation analysis include Web of Science (including its Science Citation Index), Scopus, and Google Scholar.[6] We acknowledge that Scopus and Google Scholar may provide relevant albeit different citation metrics. Compared with Web of Science, Scopus includes more journals and is convenient for keyword search and citation analysis, but its citation analysis is not sufficient.[7] Google Scholar can help retrieve even the most obscure information, but its use is marred

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by inadequate citation information that is updated less often.[6] Therefore, we chose the Web of Science (including the Science Citation Index) for our study.

MATERIALS AND METHODS

Data Sources and Searches

The Web of Science (including the Science Citation Index) database was searched using keywords such as "colorectal," "colon," "rectal," '"BD," "ulcerative colitis," "Crohn's disease," and "colonoscopy" for manuscripts relating to colorectal diseases published since 1955 (the earliest year for which data were available) to the present; more keywords are shown in Table S1. We conducted our search on August 28, 2020, to avoid possible changes in the citation rate. Sorted into the category "Times Cited," a list of the top-cited articles in the area of colorectal disease were determined. The full-text articles were obtained from PubMed, ScienceDirect, and EMBASE.

Study Selection and Data Extraction

The articles were selected by 2 researchers (C. Zhang and M. Luo), who read the abstracts to estimate whether they were related to colorectal diseases. The exclusion criteria were as follows: (1) articles in languages other than English and (2) articles focused on a wide range of areas without focusing entirely on colorectal disease.[3,8] Any discrepancy was resolved by a third investigator (H. Zhu). The 100 most-cited articles were included and analyzed. Data were extracted from each of the top-cited articles by 2 researchers (M. Luo and C. Zhang) using a predesigned Microsoft Excel template, with checks done by another researcher (J. Zhou). All the data were analyzed by 2 investigators (C. Zhang and M. Luo) with regard to authorship (only considering the first and second authors), institution, journal name, publication date, country of origin, number of citations, average citations per year, topic, study type (e.g., meta-analysis or systematic review, randomized controlled trial, prospective study, retrospective study, review, guideline, comment, or case report), and level of evidence. There are multiple methods of grading the level of evidence.[9] In our analysis, the level of evidence was determined using the Australian National Health and Medical Research Council evidence hierarchy.[10]

Main Points

- *Examination of top-cited articles is a tool that can help to identify and monitor outstanding scientific researches and landmark papers.*
- *The 100 most-cited papers in peer-reviewed biomedical journals in the field of colorectal disease are identified and analyzed.*
- *The most popular field is colorectal cancer (n = 45), followed by colon tumor (n = 21).*
- *Our study can give a historical perspective on the scientific progress of colorectal disease.*

Statistical Analysis

Tables and charts were created using Microsoft Word and Microsoft Excel, respectively. Data visualization was conducted using the VOSviewer (Leiden University, Leiden, The Netherlands) technique to create scientific landscapes and networks based on keyword frequency in titles and abstracts.

RESULTS

The top 100 most-cited articles in the field of colorectal disease between 1955 and 2017 were identified (Table 1). The number of citations ranged from 1575 to 9283, with a mean of 2504.11 citations per article.

Year, Country, and Number of Citations

The number of articles, citations per year, and country distribution are shown in Figures 1 and 2. The top 100 most-cited articles covered a wide range of countries, with the majority from the United States (n = 60), and the remainder from France (n = 10), the UK (n = 10), Canada (n = 4), the Netherlands (n = 3), Japan (n = 3), Belgium (n = 2), Denmark (n = 2), Australia (n = 1), Germany (n = 1), Finland (n = 1), Italy (n = 1), Sweden (n = 1), and Spain (n = 1) (Figure 2). The United States had the highest number of citations (n = 156 142), and Sweden had the lowest (n = 1761). These articles were published between 1955 and 2017. The earliest article was published in 1955 by Truelove et al. in the *British Medical Journal*.[11] Siegel et al.[12] had the most recent article among the 100 most-cited articles, published in 2017 in the *CA-A Cancer Journal for Clinicians*. As shown in Figure 1, from 1955 to 1988, only 7 articles were included, while more than 93% of the top-cited articles were published after 1989. For total citations, the trend per year was inconsistent with top-cited publications (Figure 1).

Authors and Journals

Fourteen authors published 2 or more articles (Table 2). Among these, Fearon authored the most papers (n = 5).

Table 1. The Top-Cited 100 Articles on Colorectal Disease

Rank	Title	No. of Citations	Average Citations Per Year
1	Fearon ER1, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; 61:759-67.	9283	309.43
2	Hurwitz H1, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335-42.	7886	492.88
3	Vogelstein B1, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal tumor development. *N Engl J Med* 1988;319:525-32.	5613	175.41
4	Muzny DM, Bainbridge MN, Chang K, et al. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012;487:330-7.	4243	530.38
5	Andersen CL1, Jensen JL, Ørntoft TF. Normalization of real-time quantitative reverse transcription-PCR data: A model-based variance estimation approach to identify genes suited for normalization, applied to bladder and colon cancer data sets. *Cancer Res* 2004;64:5245-50.	4145	259.06
6	Hugot JP1, Chamaillard M, Zouali H, et al.Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 2001;411:599-603.	4099	215.74
7	Sauer R1, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731-40.	3946	246.63
8	Kinzler KW1, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996;87:159-70.	3940	164.17
9	Cunningham D1, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337-45.	3911	244.44
10	Ogura Y1, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* 2001;411:603-6.	3654	192.32
11	Galon J1, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006;313:1960-4.	3437	245.50
12	Sjöblom T1, Jones S, Wood LD, et al. The consensus coding sequences of human breast and colorectal cancers. *Science* 2006;314:268-74.	3411	243.64
13	Morin PJ, Sparks AB, Korinek V, et al. Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. *Science* 1998;275:1787-90.	3292	143.13
14	Winawer SJ1, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. *N Engl J Med* 1993;329:1977-81.	3279	121.44
15	Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for Cancer Detection and Familial Predisposition: Development of International Criteria for the Determination of Microsatellite Instability in Colorectal Cancer. *Cancer Res* 1998;58:5248-57.	3260	148.18
16	Longstreth GF1, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006;130:1480-91.	3165	226.07
17	Ricci-Vitiani L1, Lombardi DG, Pilozzi E, et al. Identification and expansion of human colon-cancer-initiating cells. *Nature* 2007;445:111-5.	3074	236.46
18	O'Brien CA1, Pollett A, Gallinger S, et al. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. *Nature* 2007;445:106-10.	3063	235.62
19	Tetsu O1, McCormick F. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. *Nature* 1999;398:422-6.	3063	145.86
20	Hanauer SB1, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541-9.	2964	164.67
21	Groux H1, O'Garra A, Bigler M, et al. A CD4(+) T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* 1997;389:737-42.	2951	128.30
22	de Gramont A1, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;18:2938-47.	2893	144.65
23	de Gramont A1, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;18:2938-47.	2830	148.95

(*Continued*)

Table 1. The Top-Cited 100 Articles on Colorectal Disease (*Continued*)

Rank	Title	No. of Citations	Average Citations Per Year
24	Podolsky DK1. Inflammatory bowel disease. *N Engl J Med* 2002;347:417-29.	2782	154.56
25	Korinek V1, Barker N, Morin PJ, et al. Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC(-/-) colon carcinoma. *Science* 1997;275:1784-7.	2763	120.13
26	Alon U1, Barkai N, Notterman DA, et al. Broad patterns of gene expression revealed by clustering analysis of tumor and normal colon tissues probed by oligonucleotide arrays. *Proc Natl Acad Sci U S A* 1999;96:6745-50.	2754	131.14
27	Thibodeau SN1, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. *Science* 1993;260:816-9.	2725	100.93
28	Karapetis CS1, Khambata-Ford S, Jonker DJ ,et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;359:1757-65.	2650	220.83
29	Van Cutsem E1, Köhne CH, Hitre E, et al. Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer. *N Engl J Med* 2009;360:1408-17.	2634	239.45
30	Xavier RJ1, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007;448:427-34.	2628	202.15
31	Targan SR1, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. *N Engl J Med* 1997;337:1029-35.	2579	112.13
32	Douillard JY1, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000;355:1041-7.	2563	128.15
33	Aaltonen LA1, Peltomäki P, Leach FS, et al. Clues to the pathogenesis of familial colorectal cancer. *Science* 1993;260:812-6.	2560	94.81
34	Mandel JS1, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med* 1993;328:1365-71.	2524	93.48
35	Fong Y1, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer – Analysis of 1001 consecutive cases. *Ann Surg* 1999;230:309-18.	2488	118.48
36	Fishel R1, Lescoe MK, Rao MR, et al. The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. *Cell* 1993;75:1027-38.	2463	91.22
37	Saltz LB1, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2000;343:905-14.	2453	122.65
38	Jostins L1, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012;491:119-24.	2433	304.13
39	André T1, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343-51.	2398	149.88
40	Rutgeerts P1, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353:2462-76.	2392	159.47
41	Nelson H, Sargent DJ, Wieand HS, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004;350:2050-9.	2388	149.25
42	Amado RG1, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:1626-34.	2387	198.92
43	Frank DN1, St Amand AL, Feldman RA, et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci USA* 2007;104:13780-5.	2378	182.92
44	Ionov Y1, Peinado MA, Malkhosyan S, et al. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. *Nature* 1993;363:558-61.	2312	85.63
45	Molodecky NA1, Soon IS, Rabi DM, et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. *Gastroenterology* 2012;142:46-54.	2305	288.13

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Table 1. The Top-Cited 100 Articles on Colorectal Disease (*Continued*)

Rank	Title	No. of Citations	Average Citations Per Year
46	Tournigand C1, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229-37.	2262	141.38
47	Wood LD1, Parsons DW, Jones S, et al. The genomic landscapes of human breast and colorectal cancers. *Science* 2007;318:1108-13.	2244	172.62
48	Oshima M1, Dinchuk JE, Kargman SL, et al. Suppression of intestinal polyposis in Apc(Delta 716) knockout mice by inhibition of cyclooxygenase 2 (COX-2). *Cell* 1996;87:803-9.	2184	91.00
49	Eberhart CE1, Coffey RJ, Radhika A, et al. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. *Gastroenterology* 1994;107:1183-8.	2178	83.77
50	Guillou PJ1, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 2005;365:1718-26.	2173	144.87
51	Gold P, Freedman SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. *J Exp Med* 1965;121:439-62.	2164	39.35
52	Duerr RH1, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006;314:1461-3.	2148	153.43
53	Tsujii M1, Kawano S, Tsuji S, et al. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. *Cell* 1998;93:705-16.	2126	96.64
54	Saltz LB1, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol* 2008;26:2013-9.	2119	176.58
55	Leach FS1, Nicolaides NC, Papadopoulos N, et al. Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. *Cell* 1993;75:1215-25.	2105	77.96
56	Markowitz S1, Wang J, Myeroff L, et al. Inactivation of the type II TGF-beta receptor in colon cancer cells with microsatellite instability. *Science* 1995;268:1336-8.	2101	84.04
57	TRUELOVE SC, WITTS LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955;2:1041-8.	2101	32.32
58	Hardcastle JD1, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472-7.	2069	86.21
59	Sokol H1, Pigneur B, Watterlot L, et al. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn's disease patients. *Proc Natl Acad Sci USA* 2008;105:16731-6.	2058	171.50
60	Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA Cancer J Clin* 2014;64:104-17.	2033	338.83
61	Present DH1, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398-405.	1938	92.29
62	Steinbach G1, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000;342:1946-52.	1934	96.70
63	Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery – the clue to pelvic recurrence? *Br J Surg* 1982;69:613-6.	1932	50.84
64	Umar A1, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004;96:261-8.	1919	119.94
65	Silverberg MS1, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;19 Suppl A:5A-36A.	1916	127.73
66	Loftus EV Jr1. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004;126:1504-17.	1916	119.75
67	Kronborg O1, Fenger C, Olsen J,et al.Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467-71.	1902	79.25

(*Continued*)

Table 1. The Top-Cited 100 Articles on Colorectal Disease (*Continued*)

Rank	Title	No. of Citations	Average Citations Per Year
68	Bresalier RS1, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.	1899	126.60
69	Moertel CG1, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990;322:352-8.	1899	63.30
70	Siegel RL, Miller KD, Fedewa, SA, et al. Colorectal cancer statistics, 2017. *CA-A Cancer J Clinician* 2017;67:177-193.	1895	631.67
71	Barrett JC1, Hansoul S, Nicolae DL, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008;40:955-62.	1878	156.50
72	Baker SJ1, Markowitz S, Fearon ER, et al. Suppression of human colorectal carcinoma cell growth by wild-type p53. *Science* 1990;249:912-5.	1868	62.27
73	Baker SJ1, Fearon ER, Nigro JM, et al. Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. *Science* 1989;244:217-21.	1860	60.00
74	Toyota M1, Ahuja N, Ohe-Toyota M, et al. CpG island methylator phenotype in colorectal cancer. *Proc Natl Acad Sci USA* 1999;96:8681-6.	1857	88.43
75	Greten FR1, Eckmann L, Greten TF, et al. IKK beta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* 2004;118:285-96.	1845	115.31
76	Bronner CE1, Baker SM, Morrison PT, et al. Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. *Nature* 1994;368:258-61.	1834	70.54
77	Colombel JF1, Sandborn WJ, Reinisch W, et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. *N Engl J Med* 2010;362:1383-95.	1828	182.80
78	Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975;36:2251-70.	1826	40.58
79	Bosset JF1, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;355:1114-23.	1820	130.00
80	Lacy AM1, García-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. *Lancet* 2002;359:2224-9.	1793	99.61
81	Goldberg RM1, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004;22:23-30.	1782	111.38
82	Hidalgo IJ1, Raub TJ, Borchardt RT. Characterization of the human colon carcinoma cell line (Caco-2) as a model system for intestinal epithelial permeability. *Gastroenterology* 1989;96:736-49.	1772	57.16
83	Eaden JA1, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;48:526-35.	1762	92.74
84	Cedermark B, Dahlberg M, Glimelius B, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. *New Engl J Med* 1997;336:980-7.	1761	76.57
85	Bos JL, Fearon ER, Hamilton SR, et al. Prevalence of ras gene mutations in human colorectal cancers. *Nature* 1987;327:293-7.	1726	52.30
86	Vasen HF1, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch Syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology* 1999;116:1453-6.	1725	82.14
87	Fearon ER, Cho KR, Nigro JM, et al. Identification of a chromosome 18q gene that is altered in colorectal cancers. *Science* 1990;247:49-56.	1721	57.37
88	Papadopoulos N1, Nicolaides NC, Wei YF, et al. Mutation of a mutL homolog in hereditary colon cancer. *Science* 1994;263:1625-9.	1719	66.12
89	Giantonio BJ1, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007;25:1539-44.	1716	132.00

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Table 1. The Top-Cited 100 Articles on Colorectal Disease (*Continued*)

Rank	Title	No. of Citations	Average Citations Per Year
90	Fiocchi C1. Inflammatory bowel disease: Etiology and pathogenesis. *Gastroenterology* 1998;115:182-205.	1695	77.05
91	Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;1:1479-82.	1692	49.76
92	Franke A, McGovern DPB, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet* 2010;42:1118-+.	1677	167.70
93	Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. *Gut* 1999;45:43-47.	1673	79.67
94	Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: Clinical guidelines and rationale - Update based on new evidence. *Gastroenterology* 2003;124:544-60.	1670	98.24
95	Okayasu I1, Hatakeyama S, Yamada M, et al. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. *Gastroenterology* 1990;98:694-702.	1669	55.63
96	Lièvre A1, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 2006;66:3992-5.	1659	118.50
97	Lennard-Jones JE1. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989;170:2-6.	1649	53.19
98	Solomon SD1, McMurray JJ, Pfeffer MA, Wittes J, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med* 2005;352:1071-80.	1597	106.47
99	Cooper HS, Murthy SN, Shah RS, et al. Clinicopathologic study of dextran sulfate sodium experimental murine colitis. *Laboratory Investigation J Tech Methods Pathol* 1993;69:238-49.	1586	58.74
100	Nishisho I1, Nakamura Y, Miyoshi Y, et al. Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. *Science* 1991;253:665-9.	1575	54.31

Twenty-one journals made contributions to the top-cited articles. The journals with the highest impact factor (IF) included the *New England Journal of Medicine (NEJM)* (IF = 74.699), *Science* (IF = 41.845), *Nature* (IF = 42.778), *Gastroenterology* (IF = 17.373), *Cell* (IF = 38.637), the *Lancet* (IF = 60.392), and the *Journal of Clinical Oncology* (IF = 32.956). Among them, 23 articles were published in *NEJM* (n = 64 941 citations), 14 in *Science* (n = 33 424 citations), 12 in *Nature* (n = 35 080 citations), 9 in *Gastroenterology* (n = 18 059), 7 in *Cell* (n = 23 946 citations), 7 in the *Lancet* (n = 15 156), and 6 in the *Journal of Clinical Oncology* (n = 13 159 citations). In addition, 9 journals published only 1 article (Table 3).

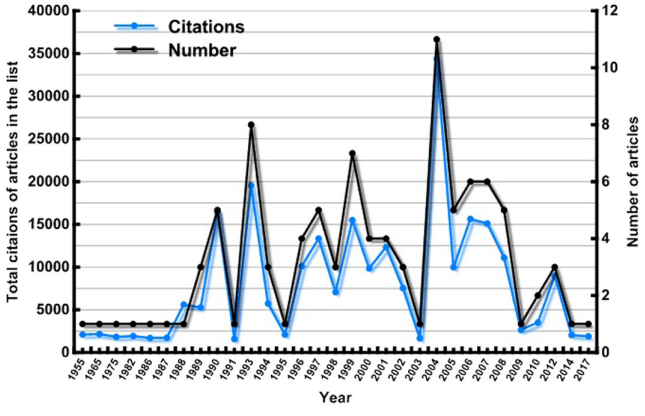

Figure 1. The number and total citations of articles per year in the top 100 most-cited articles.

Institutions

With regard to institutions, the Johns Hopkins University School of Medicine published the largest number of

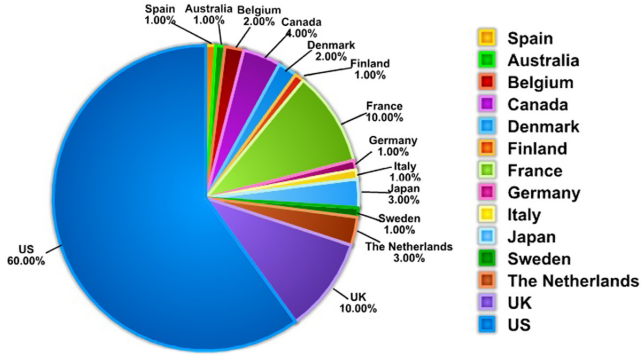

Figure 2. The number of the top 100 most-cited articles in different countries.

Table 2. Authors with Two or More Most-Cited Articles

Author	Articles	First Author	Second Author
Fearon, E R	5	2	3
Vogelstein, B	3	1	2
Andre, T	2	1	1
Baker, S J	2	2	0
Boland, CR	2	1	1
Cunningham	2	1	1
Hanauer, SB	2	1	1
Heald, R J	2	2	0
Longstreth, G F	2	1	1
Markowitz, S	2	1	1
Nicolaides, N C	2	0	2
Rutgeerts, P	2	1	1
Saltz	2	2	0
Sandborn, WJ	2	0	2

articles (n = 12). The Harvard Medical School ranked second in the number of articles published (n = 5). The Mayo Clinic, the Memorial Sloan-Kettering Cancer Center, and the University of California contributed 3 papers each. There were 6 institutions with 2 papers, while other organizations had only 1 article each (Table 4).

Top Keywords and Research Directions Related to Colorectal Disease

There were 53 keywords that were used at least 5 times. The most commonly used keywords were cancer (n = 52), gene (n = 25), mutation (n = 21), tumor (n = 20), data (n = 19), cell (n = 17), colon (n = 14), colon cancer (n = 14), Crohn's disease (n = 14), role (n = 14), combination (n = 13), inflammatory bowel disease (n = 13), metastatic colorectal cancer (n = 13), overall survival (n = 13), progression (n = 13), week (n = 13), fluorouracil (n = 12), primary end point (n = 12), ulcerative colitis (n = 12), and chromosome (n = 11). The top-cited keywords among these are demonstrated in Figure 3. Among these 100 classic articles, each article contains multiple research directions (with a total of 34 research directions), of which *gastroenterology hepatology* is the most researched, with 48 articles. This is followed by *oncology* (n = 44), *biochemistry molecular*

Table 4. Institution with the Highest Number of Papers in the 100 Most-Cited Articles

Institution	No. of Articles
The Johns Hopkins University School of Medicine	12
Harvard Medical School	5
Mayo Clinic	3
Memorial Sloan-Kettering Cancer Center	3
University of California, San Diego	3
Amer Canc Soc	2
University Hospitals of Cleveland	2
Vanderbilt University Medical Center	2
University of Texas M.D. Anderson Cancer Center	2
The North Hampshire Hospital	2
Hopital Saint-Antoin	2
Others	62

Table 3. Journals in Which the 100 Most-Cited Articles Were Published

Journal Title	Number of Manuscripts in the 100 Citation Classics	Number of Citations	Average Number of Citations	Impact Factor[a]
The New England Journal of Medicine	23	64 941	2823.52	74.699
Science	14	33424	2387.43	41.845
Nature	12	35 080	2923.33	42.778
Gastroenterology	9	18 059	2010.56	17.373
Cell	7	23 946	3420.85	38.637
Lancet	7	15 156	2165.14	60.392
Journal of Clinical Oncology	6	13 159	2193.17	32.956
Proceedings of the National Academy of Sciences of the United States of America	4	9047	2261.75	9.412
Cancer Research	3	9064	3021.33	9.727
Others[b]	15	28 499	1899.93	-

[a]Journal impact factor was based on Thomson Reuters Web of Knowledge Journal Citation Reports Ranking (2019).
[b]Journals with 1 or 2 most-cited articles.

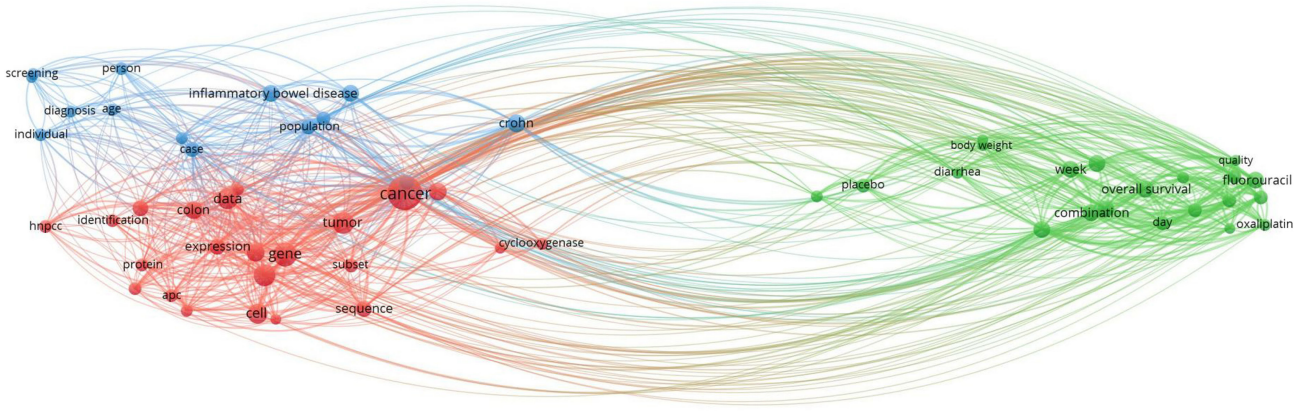

Figure 3. Top used keywords related to colorectal disease in the top 100 most-cited articles.

biology (n = 26), *genetics heredity* (n = 23), *general internal medicine* (n = 22), *cell biology* (n = 21), *science technology other topics* (n = 16), and *geriatrics gerontology* (n = 10). There were 26 research directions with fewer than 10 articles, and 10 research directions appeared only once (Figure S1).

Research Area, Study Type, Level of Evidence

In terms of the research area, 72 articles focused on tumors. Among them, 45 papers (45%) involved colorectal tumors, 21 (21%) colon tumors only, and 6 (6%) rectal tumors only. The remaining 22 papers concentrated on colorectal inflammation, of which 9 (9%) papers were on Crohn's disease, 3 (3%) on ulcerative colitis, and 10 (10%) on inflammatory bowel disease. Regarding study type, there were basic science studies (n = 43), randomized controlled trials (n = 30), reviews (n = 12), prospective studies (n = 3), guidelines and consensus (n = 2), retrospective studies (n = 1), case reports (n = 2), and meta-analyses (n = 1) (Table 5). The types of clinical studies and level of evidence in the top-cited articles are summarized in Table 6. There were 5 studies at level I, 29 at level II, and 5, 1, and 15 studies at levels III, IV, and V, respectively.

DISCUSSION

The worldwide incidence of colorectal diseases, especially colorectal cancer and inflammatory bowel disease, has increased in recent years.[13] Therefore, a great deal of research has been done on colorectal diseases, including pathogenesis, epidemiology, genetics, and immunology. The number of citations of an article on a certain subject represents the influence and credibility of that article, and it also indicates the author's academic achievement.[14] At present, the most-cited articles have been widely used in gastric diseases, hepatology, urology,[3-5] and other disciplines. For diseases of the digestive system, analysis of the top-cited articles has been performed in gastric cancer,[15] acute pancreatitis,[16] and ulcerative colitis.[17] However, no study has reported the most-cited articles in the field of colorectal diseases. Therefore, we aimed to analyze the characteristics of the 100 top-cited articles on colorectal diseases.

We found that the number of citations in colorectal disease literature was higher than that for some other digestive diseases, such as gastric cancer (n = 299-2893) and acute pancreatitis (n = 163-1281),[15,16] which confirms that colorectal diseases are a hot topic. In terms of country of origin and journal of publication, the citation characteristics for articles on colorectal diseases and other gastrointestinal diseases were similar. For example, the top-cited articles were primarily distributed in the United States, research on inflammatory conditions was mainly published in *Gastroenterology*, and cancer studies were generally published in *NEJM*.[15-17]

In our study, the articles were distributed in various countries, with the United States occupying first place. In addition to having the most-cited articles every year, the United States also ranked first in the number of articles almost every year since 1986. The reasons for that may be as follows. First, a number of studies indicate that healthcare expenditure is closely linked to a country's economic power, and the United States has the largest economy in the world. Second, it reflects the abundant funding support provided by the National Institutes of Health (25.29%), Health and Human Services (24.51%), the National Cancer Institute (11.67%), and other public and private sector agencies (Table S2). Finally, the United

Table 5. Field of Study Based on Types of Studies

Name of Disease	Total	Clinical Study				Case Report	Basic Science Study	Review	Guideline and Consensus	Meta-Analysis or Systematic Review	Others
		RCTs	Prospective Study	Retrospective Study							
Tumor											
Only colon cancer	21	4	-	-		-	17	-	-	-	-
Only rectal cancer	6	4	-	-		2	-	-	-	-	-
Colorectal cancer	45	16	2	1		–	15	7	2	1	1
Inflammation											
IBD	10	-	-	-		-	3	3	-	1	3
Only UC	3	1	1	-		-	1	-	-	-	-
Only CD	9	4	-	-		-	4	-	-	1	-
Colorectal polypi	2	1	-	-		-	1	-	-	-	-
Functional Bowel Disorders	2	-	-	-		-	-	2	-	-	-
Colitis	2	-	-	-		-	2	-	-	-	-
Total	100	30	3	1		2	43	12	2	3	4

RCTs, randomized controlled trials.

Table 6. Levels of Evidence and Article Type Comprising the 100 Most-Cited Articles

Level of Evidence	Article Type	No. of Articles
I	Systematic review	1
	Meta-analysis	1
	Guidelines	3
II	Randomized controlled trial	29
III	Prospective study	5
IV	Retrospective study	1
V	Case Reports	1
	Review	13
	Comment	1

States has a rewards system for academia that encourages researchers to conduct basic and clinical studies, leading to such a substantial research contribution.[18]

Colorectal cancer was the third most commonly diagnosed cancer in males and the second most commonly diagnosed cancer in females in developed countries, based on global cancer statistics in 2018.[13] In this study, we discovered that research on colorectal cancer accounted for a large proportion of the 100 landmark articles, which mainly concentrated on drugs and surgery. The combination of biological agents and chemotherapy was one of the hot topics in these 100 most-cited articles.[19,20] These included bevacizumab, cetuximab, the LV5FU2–oxaliplatin combination, fluorouracil-based combination chemotherapy, and irinotecan combined with fluorouracil and calcium folinate. Two articles indicated that laparoscopic surgery was better than open surgery for postoperative morbidity, hospitalization time, tumor recurrence, and cancer-related survival.[21,22] One study demonstrated that preoperative chemoradiotherapy for colorectal cancer had a good effect on local control, but it did not affect the overall survival rate.[23] In addition, several most-cited articles emphasized the importance of early diagnosis or screening of colorectal cancer and precancerous lesions using different modalities. The screening methods, including fecal occult blood testing with rehydration of the samples,[24] stool DNA tests,[25] and double-contrast barium enemas,[25] were mentioned in the 100 classic articles. The occurrence of colorectal cancer would be largely prevented by endoscopic resection if precancerous lesions, such as adenomatous polyps, were detected in screening.[26]

Research related to genetics in colorectal cancer is also important, including oncogene activation (*K-RAS* and

EGFR),[20,27] tumor suppressor gene inactivation (*P53*),[27] mismatch repair gene mutations (*hMSH2*, *PMS1*, and *PMS2*),[28] and excessive gene expression (*COX-2* and *CD33*).[29,30] From an etiological perspective, patients with familial adenomatous polyposis have a nearly 100% risk of colorectal cancer.[31] There were various stages of hyperplasia, adenoma, and cancerization in terms of morphological and corresponding chromosomal changes (*5q*, *17p*, and *18q*).[32] These studies indicate that the development and progression of colorectal cancer is a multistage process with multiple gene mutations, which is currently the consensus among gastroenterologists.

The 100 top-cited articles were mainly published in 19 journals, which published the highest number of papers in these fields at the fastest speed and with the strictest standards. Most of the articles were published in *NEJM*. The reasons may be as follows. First, *NEJM*, a medical journal published by the American Massachusetts Medical Society, has published medical papers continuously for the longest time in the world. Second, *NEJM* is one of the most authoritative medical journals with a high impact factor (79.258 in 2017) and it has become the preferred choice of publication by excellent scholars worldwide. *Science* and *Nature*, both of which enjoy high reputations globally, also published many top-cited articles. These 3 kinds of journals mentioned above covered more than half of the articles in the classic citations of colorectal disease. *NEJM* was the main source of most clinical research, while *Science* and *Nature* were the main sources of basic research.

Different study designs could correspond to different levels of evidence, and assessing the levels of evidence helps guide clinical research and patient treatment. In our study, 61.8% of the articles were at levels I and II, of which RCTs accounted for 85.3%. Therefore, the majority of clinical trials among the top 100 cited articles were well designed. However, there were also 5, 1, and 15 studies at levels III, IV, and V, respectively; thus, more high-quality RCTs should be conducted in the field of colorectal diseases in the future.

We acknowledge that there were some limitations to this study. First, the articles in this field might not have been sought out entirely owing to the differences in the keywords and the insensitivity of the database search. We made efforts to input multiple combinations of colorectal disease keywords in Web of Science to detect as many relevant articles as possible. Second, we merely screened the articles published in English; hence papers with significance in other languages might have been missed. Third, the composition of the ranking list and the comparative 'order and degree' of publications are dynamic and constantly changing. Therefore, the 100 most-cited articles obtained at different times may vary, but the general trend will not change.

In conclusion, the study reviewed the 100 most-cited articles that reflected research progress and hot topics in the last 60 years in the field of colorectal disease, and the articles of significant findings that have contributed greatly to the occurrence and treatment of colorectal disease were confirmed. Therefore, these 100 most highly cited articles are meaningful for new researchers in understanding this field over a long period and are also helpful for researchers when searching for literature.

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Informed Consent: N/A.

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Author Contributions: Concept – C.Z., M.L., L.M.; Design – C.Z., M.L.; Supervision – H.Z., J.Z.; Fundings – L.M.; Materials – C.Z., M.L.; Data Collection and/or Processing – C.Z., M.L.; Analysis and/or Interpretation – C.Z., M.L.; Literature Search – C.Z., M.L.; Writing Manuscript – C.Z., M.L.; Critical Review – H.Z., J.Z., L.M.

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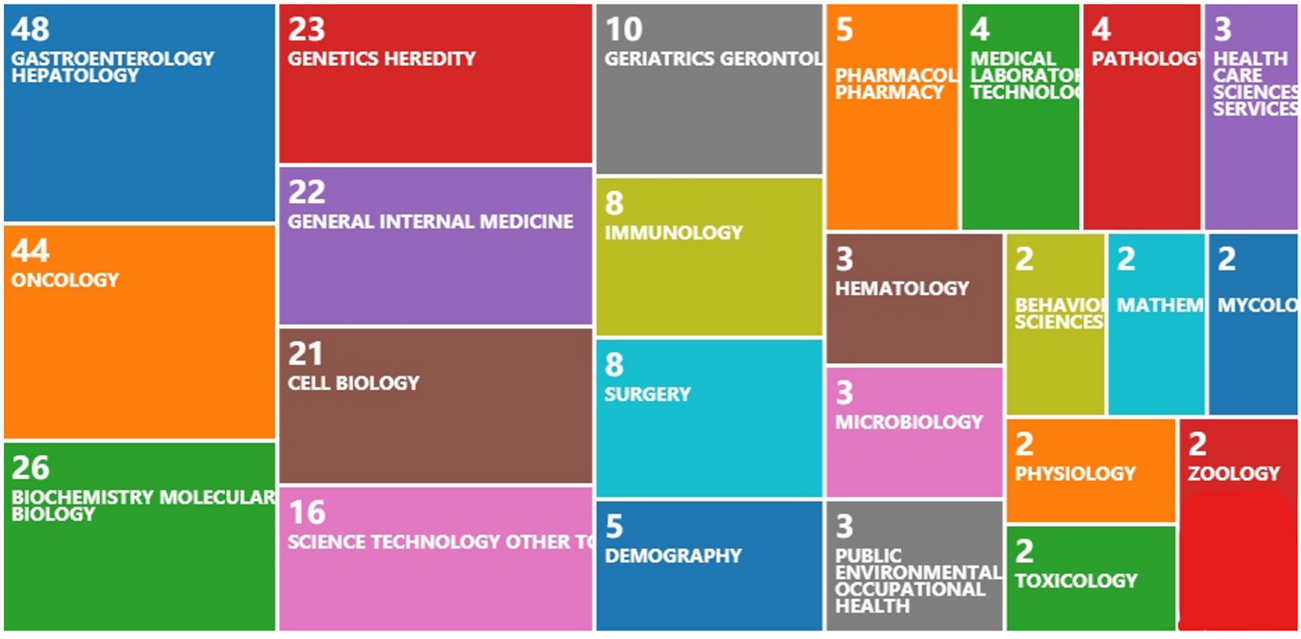
Supplementary Table 1. The Search Words Used in Our Study

Colorectal	Colon	Rectal	IBD
Ulcerative colitis	Crohn's disease	Colonoscopy	Diverticulosis
Diverticulitis	Infectious colitis	Radiation colitis	Cytomegalovirus colitis
Tuberculosis colitis	Campylobacter colitis	Shigella colitis	Ischemic colitis
Microscopic colitis	Colonic polyps	Colonic perforation	Bleeding per rectum



Supplementary Figure 1. Number of the top 100 most-cited articles in different research directions (at least 2 articles have been published in this research direction).

Supplementary Table 2. Funding Resources for the 100 Most-Cited Articles

Funding Resources	N (%)
NIH, United States	65 (25.29)
HHS, United States	63 (24.51)
NCI, United States	30 (11.67)
NIGMS, United States	11 (4.28)
NIDDK, United States	9 (3.5)
NIAID, United States	4 (1.56)
NCRR, United States	3 (1.17)
NHGRI, United States	3 (1.17)
Medical Research Council, United Kingdom	3 (1.17)
NIEHS, United States	2 (0.78)
Wellcome Trust, United Kingdom	2 (0.78)
National Association for Colitis and Crohn's disease, United Kingdom	2 (0.78)
Chief Scientist Office, Scotland	2 (0.78)
Crohn's & Colitis Foundation of America, United States	2 (0.78)
Crohn's and Colitis Foundation, United Kingdom	2 (0.78)
Alberta Heritage Foundation for Medical Research, Canada	2 (0.78)
NHS Research Scotland Career Fellowship, Scotland	1 (0.39)
Peninsula College of Medicine and Dentistry, United Kingdom	1 (0.39)
Biomedical Research Centre, United Kingdom	1 (0.39)
Saint Thomas' National Health Service Trust, United Kingdom	1 (0.39)
King's College London, United Kingdom	1 (0.39)
Addenbrooke's Hospital, University of Cambridge School of Clinical Medicine, United Kingdom	1 (0.39)
University of Manchester, United Kingdom	1 (0.39)
Central Manchester Foundation Trust, United Kingdom	1 (0.39)
UK National Blood Service, United Kingdom	1 (0.39)
USPHS, United States	1 (0.39)
Cedars-Sinai F. Widjaja Inflammatory Bowel and Immunobiology Research Institute Research Funds, United States	1 (0.39)
Netherlands Organization for Scientific Research, The Netherlands	1 (0.39)
UCLA/Cedars-Sinai/Harbor/Drew Clinical and Translational Science Institute (CTSI), United States	1 (0.39)
Southern California Diabetes and Endocrinology Research Grant (DERC), United States	1 (0.39)
Helmsley Foundation, United States	1 (0.39)
Celiac Disease Consortium, The Netherlands	1 (0.39)
German Ministry of Education and Research through the National Genome Research Network, Germany	1(0.39)
Popgen biobank, through the Deutsche Forschungsgemeinschaft (DFG) Cluster of Excellence ' Inflammation at Interfaces, Germany	1 (0.39)
DFG, Germany	1 (0.39)
Else Kroner-Fresenius-Stiftung (Else Kroner-Exzellenzstipendium), United Kingdom	1 (0.39)
Italian Society for Paediatric Gastroenterology, Hepatology and Nutrition, Italy	1 (0.39)
Italian Ministry of Health, Italy	1 (0.39)
Swedish Society of Medicine, Sweden	1 (0.39)

(*Continued*)

Supplementary Table 2. Funding Resources for the 100 Most-Cited Articles (*Continued*)

Funding Resources	N (%)
Ihre Foundation, Sweden	1 (0.39)
Orebro University Hospital Research Foundation, Sweden	1 (0.39)
Karolinska Institutet, Sweden	1 (0.39)
Swedish National Program for IBD Genetics, Sweden	1 (0.39)
Swedish Organization for IBD, Sweden	1 (0.39)
Swedish Medical Research Council, Sweden	1 (0.39)
Royal Brisbane and Women's Hospital Foundation, Australia	1 (0.39)
European Community (5th PCRDT), Europe	1 (0.39)
National Institute of Child Health and Human Development (NICHD), United States	1 (0.39)
Juvenile Diabetes Research Foundation (JDRF), United States	1 (0.39)
Helmholtz Zentrum Munchen-German Research Center for Environmental Health, Germany	1 (0.39)
German Federal Ministry of Education and Research (BMBF), Germany	1 (0.39)
State of Bavaria, Germany	1 (0.39)
Academy of Medical Sciences (AMS), United Kingdom	1 (0.39)
Arthritis Research UK, United Kingdom	1 (0.39)
Alberta IBD Consortium, Canada	1 (0.39)
Assistance Publique-Hopitaux de Paris, French	1 (0.39)
Canadian Institute of Health Research, Canada	1 (0.39)
Damon Runyon Cancer Research Foundation, United States	1 (0.39)
Jane Coffin Child's Memorial Fund	1 (0.39)
Merck (Darmstadt), Germany	1 (0.39)
National Basic Research Program of China, China	1 (0.39)
National Natural Science Foundation of China, China	1 (0.39)
Natural Science Foundation of Jiangsu Province, China	1 (0.39)
NCEH, United States	1 (0.39)
Telethon, Australia	1 (0.39)
Roche, Switzerland	1 (0.39)
PHS, New Mexico	1 (0.39)
Sanofi-Aventis, United States	1 (0.39)