PASS information

Title	A Non-Interventional Observational Longitudinal Post Authorization Safety Study (PASS) of SIMPONI® in Treatment of Ulcerative Colitis using Nordic National Health Registries
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Marketing authorisation holder(s)	Janssen Biologics B.V.
Joint PASS	No
Research question and objectives	This study addressed whether, in ulcerative colitis (UC) patients with similar baseline disease characteristics, the use of golimumab (GLM) is associated with the risk of incident colorectal cancer (CRC), incident all-cause total colectomy (TC), and incident hepatosplenic T-cell lymphoma (HSTCL) as compared with alternative therapies. In this study, no prior research hypotheses were formulated. **Primary objectives** 1. To characterize the clinical and demographic profile of first-time users of GLM in the treatment of UC, compared with the corresponding profile of first-time users of alternative therapies 2. To describe the risk of the following endpoints in patients exposed to GLM or exposed to alternative therapies:

	2a. Incident CRC 2b. Incident All-cause TC 3. If baseline characteristics suggest comparability, to estimate 3a. The risk of incident CRC associated with GLM use relative to that associated with alternative therapies 3b. The risk of incident all-cause TC associated with GLM use relative to that associated with alternative therapies **Exploratory objective** To describe the risk of incident HSTCL associated with exposures of interest
Country(-ies) of study	Denmark; Sweden
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- Elements referring to descriptive analyses start with a 'D' (Annex 2A);
- Elements referring to the primary association analyses start with 'P' (Annex 2B)
- Elements referring to sensitivity analyses start with 'S' (Annex 2C)

At the end of the name 'DK' refers to Danish results whereas 'SE' refers to Swedish results.

The main text of the report is supported by extracts from the material in the Annexes and additional summaries as relevant. These elements are named Text Tables and Text Figures. Similarly, summarizing tables in the Abstract are named Abstract Tables.

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1 ABSTRACT

Title

A Non-interventional Observational Longitudinal Post Authorization Safety Study (PASS) of SIMPONI® in Treatment of Ulcerative Colitis (UC) using Nordic National Health Registries

Date of the report: 13 May 2024 (v2.0)

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Keywords

Simponi™, golimumab, ulcerative colitis, colorectal cancer, colectomy

Rationale and background

Simponi received European marketing authorization for treatment of moderately to severely active ulcerative colitis (UC) on 19 September 2013. This registry-based study was established to provide additional information on colorectal cancer (CRC), colectomy, and hepatosplenic T-cell lymphoma (HSTCL), as outlined in the Risk Management Plan for SIMPONI® that was approved with authorization of the UC indication.

This study used data from nationwide health registries in Denmark (DK) and Sweden (SE). To provide context for interpreting the long-term safety data on UC patients treated with golimumab (GLM), this study also followed patients with UC treated with alternative therapies for UC, including non-biologic and biologic therapies.

UC is a severe, relatively frequent and life-long disease that may be associated with severe symptoms and impaired quality of life. In the case of intractable disease, colectomy may be indicated. Patients with UC are at increased risk of developing cancer of the colon and rectum compared to the general population.

Research question and objectives

This study addressed whether, in UC patients with similar baseline characteristics, the use of GLM is associated with the risk of CRC, all-cause total colectomy (TC), and HSTCL as compared with alternative therapies for moderate-to-severe UC.

Primary objectives

1. To characterize the clinical and demographic profile of first-time users of GLM in the treatment of UC, compared with the corresponding profile of first-time users of alternative therapies.

2. To describe the risk of the following endpoints in patients exposed to GLM or exposed to alternative therapies

    2a. Incident CRC

    2b. Incident all-cause TC

3. If baseline characteristics suggest comparability, to estimate

    3a. The risk of incident CRC associated with GLM use relative to that associated with alternative therapies

    3b. The risk of incident all-cause TC associated with GLM use relative to that associated with alternative therapies

Exploratory objective

To describe the risk of incident HSTCL associated with exposures of interest.

Study design

This study was a long-term observational (non-interventional) post-authorization safety study (PASS). It used a new user cohort design and was based on registry data that were primarily collected for administrative reasons, such as reimbursement and organizational management, and not primarily for clinical purposes. GLM cohort and two comparator cohorts were created and followed up prospectively:

- A therapy cohort of UC patients treated with GLM (GLM Cohort): this cohort comprised all patients registered as new users of GLM since 19 September 2013.
- A therapy comparator cohort of UC patients treated with anti-tumor necrosis factor (TNF) therapies other than GLM (Other Anti-TNF cohort): this cohort comprised patients initiating since 19 September 2013 one of the anti-TNF therapies approved for the treatment of UC (infliximab (IFX) and adalimumab (ADA)).
- A therapy comparator cohort of UC patients treated with a thiopurine (TP), azathioprine (AZA) or 6-mercaptopurine (6-MP) (TP Cohort): this cohort comprised patients initiating since 19 September 2013 first-time therapy with TP (AZA or 6-MP), which are non-biologic immunomodulating therapies.

A patient could switch between cohorts if the qualification criteria for entering another cohort were met after entering a specific cohort. Particularly for all-cause TC as the outcome patients could leave a cohort because of discontinuation of exposure, then have a subsequent re-entry to the same or another cohort by reuptake of the same or another therapy. Patients in each

cohort were followed for the outcomes of CRC, all-cause TC, and HSTCL. The data extraction ended on 31 October 2021 and the last date for outcomes recorded in patient registries (i.e., patient registration systems) was 18 September 2021 in DK and 31 December 2020 in SE.

Setting

Study base: Patients with UC and relevant therapy ascertained from the health registers

The identification of patients with UC in DK and SE was based on the centralized patient registration system for all inpatient and outpatient encounters registered with UC (International Classification of Diseases (ICD)-10 code K51.0-K51.9) as the primary discharge diagnosis. In operational terms, the date of diagnosis of UC was taken as the earliest date recorded in an encounter where UC had been recorded as the primary discharge diagnosis.

Therapy cohorts: UC patients treated with GLM and alternative therapies

In DK and SE, patients with moderate-to-severe UC are managed exclusively by specialists with competence in gastroenterology in hospitals and hospital-based ambulatory clinics. Immunomodulatory and anti-TNF therapies are prescribed only in these settings. Registrations initiating new anti-TNF therapies or TP formed the basis for first-time inclusion in the therapy cohorts of interest (GLM cohort, Other Anti-TNF cohort and TP cohort). Subsequently, patients may change therapies. In the analysis, the consequences of switches in terms of exposure time and risk windows for the therapies of interest were managed as described in Section 9.8.2.

Patients and study size

A total of 12,646 patients (DK: 5,177; SE: 7,469) were enrolled. Abstract Table 1 shows the distribution of unique patients according to entry to the *first* therapy cohort (at initial entry to the study):

Abstract Table 1. Number of unique patients in DK and SE distributed by initial therapy cohort

	GLM cohort number	Other Anti-TNF cohort number	TP cohort number	Total number
DK	199	2,630	2,348	5,177
SE	151	2,172	5,146	7,469
Total	350	4,802	7,494	12,646

Abstract Table 2 shows the distribution of the patients represented in each therapy cohort (including those who switched therapies during follow-up) and corresponding person-years (PY) from first entry to a cohort and end of follow-up by country and according to the therapy cohort.

Abstract Table 2. Number of patients (with corresponding person-years from first entry to the cohort specified and until end of follow-up) in DK and SE represented in each therapy cohort

	GLM cohort number (PY)	Other Anti-TNF cohort number (PY)	TP cohort number (PY)	Total[a] Number (PY)
DK	595 (2,001.4)	3,676 (13,385.3)	2,348 (10,288.4)	6,619 (25,675.1)
SE	298 (1,285.7)	3,385 (11,247.4)	5,146 (19,803.5)	8,829 (32,336.6)
Total	893 (3,287.1)	7,061 (24,632.7)	7,494 (30,091.9)	15,448 (58,011.7)

Abbreviations used: PY: person-years
[a]A given patient may contribute to more than one cohort after switching therapies.

Variables and data sources

Exposures

The main exposure of interest was therapy with GLM in patients with moderate-to-severe UC, compared with exposure to alternative therapies for moderate-to-severe UC, including: (1) Other Anti-TNF therapies (IFX or ADA) and (2) TP (AZA or 6-MP). Over the course of time, UC patients who initiated GLM may have received or may later receive comparator therapies in various sequences. In operational terms, risk windows of exposure times have been created for GLM as monotherapy, Other Anti-TNF study therapies as monotherapy, GLM combined with Other Anti-TNF study therapies when the risk window was overlapping after therapy switching between GLM and Other Anti-TNF study therapies, and TPs as monotherapy. Due to limited number in the overlapping category, it was combined with GLM category in the analyses. History of therapy with vedolizumab was an exclusion criterion for entry to the TP cohort but not to the GLM and the Other Anti-TNF cohorts. History of therapy with Other Anti-TNF therapies that were neither study therapies nor authorized for treatment of UC (i.e. etanercept and certolizumab pegol) was an exclusion criterion for cohort entry for all study therapy cohorts. Vedolizumab and/or anti-TNF therapies other than study drugs were not considered a censoring event.

Outcomes

The primary outcomes comprise:

- Incident CRC
- Incident all-cause TC

The exploratory outcome is:

- Incident HSTCL

Data Sources

- Nationwide central patient registration systems in DK and SE were used to identify the study base population of patients with UC.

- Nationwide central patient registration systems and prescription registries were used to identify the GLM therapy cohort and the therapy comparator cohorts.
- Nationwide health registries (hospital activity registries, prescription registry, cancer registries) were used to ascertain outcomes and changes in therapy. Cancer registries were used to validate the ascertainment of cancers.
- Deaths were captured from the Civil Registration Services in DK and SE. Death was treated as a censoring event.
- Data from the various sources were linked at individual patient level using the unique personal identification number (PIN) assigned to all citizens in DK and SE.

Covariates

The associations between exposures and outcome were adjusted by covariates in the domains of demography (age, sex, calendar time), clinical characteristics (extent of UC, comorbidities including sclerosing cholangitis, psoriasis, arthropathies, Crohn's disease (CD)), history of relevant therapies (therapy with steroids, non-biologic therapies, biologic therapies other than the study therapies including vedolizumab), and interventions other than outcomes (lower endoscopies). Status concerning treatments with study therapies and covariates was assessed on a daily basis for each study patient from first cohort entry through end of observation and updated as relevant in case of changes.

Primary analyses

The primary analyses used Poisson regression methods for occurrence of outcomes (CRC and all-cause TC) in relation to underlying person-time at risk until outcome or censoring. For each outcome, GLM therapy was first contrasted with Other Anti-TNF therapy and then with TP therapy.

The risk time with exposure for both GLM and Other Anti-TNF was originally planned to be handled as a separate overlap category; however, the overlap category was instead allocated to GLM therapy due to small number of outcomes.

Adjusted analyses were performed for the full set of covariates as well as for a subset of covariates judged to be of relevance for the CRC and all-cause TC outcomes by a panel of clinical experts in a directed acyclic graph (DAG) process.

Sensitivity analyses

Various sensitivity analyses were carried out representing alternative ways of defining risk windows, patient inclusion criteria and outcomes. The sensitivity analyses also included a probabilistic quantitative bias analysis (QBA) to adjust for the under-reporting of exposure to prior IFX in the Swedish national patient register as well as an analysis using capture-recapture methodology to investigate the validity of ascertaining incident cases of CRC in SE.

Results

During the enrolment period and follow-up, 68 cases of CRC (DK: 27; SE: 41) and 1,160 cases of all-cause TC (DK: 686; SE: 474) were registered. Among the all-cause total colectomies registered, 522 (76%) in DK and 275 (58%) in SE occurred in risk windows with exposure for one or more study therapies and were included in the primary association analyses. No cases of HSTCL were identified.

The number of incident cases of CRC in exposure categories was so small that detailed presentation of the results had to be masked due to rules implied by the General Data Protection Regulation (GDPR). However, 95% confidence intervals (CIs) were large and included the unity value of 1. Accordingly, there was no evidence to support that GLM conferred a higher risk of CRC when compared with Other Anti-TNF therapies and with TP. The results were largely unaffected by adjustment with covariates. Furthermore, there was no evidence of a difference in risk of CRC between the DK and SE populations.

In the descriptive analyses, the Danish patients in the total population of unique patients included in the study had an incidence rate (IR) of all-cause TC (33.1 per 1,000 PYs (95% CI: 30.6, 35.6)) that was statistically significantly higher than for the Swedish patients (IR 17.6 per 1,000 PYs (95% CI: 16.1, 19.3)). The data suggested that the difference in the IR of all-cause TC between DK and SE was predominantly seen for patients on therapy with biologics, as there was no statistically significant difference among patients exclusively on TP therapy.

In the primary association analysis with all-cause TC as the outcome there was a slightly increased risk for GLM therapy as compared with therapy with Other Anti-TNFs. In DK, the crude incidence rate ratio (IRR) was 1.5 (95% CI: 1.2, 1.9) and the fully adjusted estimate was 1.3 and was marginally statistically significant (95% CI: 1.0, 1.6). In SE, the crude IRR was 1.4 (95% CI: 0.9, 2.3) and the fully adjusted estimate was 1.1 (95% CI: 0.7, 1.8), and both were not statistically significant.

When comparing GLM with TP therapy, there was an increased IRR of all-cause TC for GLM therapy. In DK, the crude IRR was 10.4 (95% CI: 6.7, 16.0) and the fully adjusted estimate was 12.7 (95% CI: 8.1, 19.8). In SE, the crude IRR was 4.4 (95% CI: 2.7, 7.0) and the fully adjusted estimate was 3.9 (95% CI: 2.3, 6.4). The crude results remained largely unaffected by adjustment.

A meta-analysis using the Mantel-Haenszel (M-H) method was used to obtain weighted estimates based on aggregated data from DK and SE and to investigate the possible heterogeneity between the results from the two countries.

For the all-cause TC outcome, there was no evidence of heterogeneity between DK and SE concerning the comparison between GLM and Other Anti-TNF. The weighted M-H estimate was 1.5 (95% CI: 1.2, 1.8), which is close to the country-specific crude estimates described above, and there was no evidence of heterogeneity between the two countries.

When comparing GLM with TP, the IRRs differed markedly between DK and SE as described above. In the meta-analysis, the weighted M-H estimate was 7.8 (95% CI: 5.7, 10.9) and with strong statistical evidence of heterogeneity (I^2 value as high as 86.1% and P=0.007 for Q-test for heterogeneity) by country. Even though the IR for GLM was twice as high in DK compared

with SE, the IR for TP was close to each other in the two countries. It must be noted that the IRs shown in these analyses ignored person-time without exposure.

The sensitivity analyses related to CRC as the outcome could not be presented due to masking rules. For all-cause TC as the outcome, most of the sensitivity analyses representing alternative ways of defining risk windows, patient inclusion criteria and outcomes were not different from the primary analyses with a few exceptions. In the QBA, a reduction of about 30% was observed in the risk of all-cause TC after adjusting for prior IFX exposure, indicating some degree of bias against GLM due to the under-ascertainment of prior IFX exposure in SE.

Discussion

In this observational study, using nationwide routinely collected data from health registers in SE and DK, there was no evidence that therapy with GLM conferred an increased risk of CRC when compared with therapy with Other Anti-TNFs (IFX and ADA) and therapy with TP, respectively. However, due to the small number of incident cases with CRC (in total, 27 and 41 incident cases in DK and SE, respectively), the detailed results could not be presented.

For all-cause TC as the outcome, there was a slightly increased crude IRR for therapy with GLM versus therapy with Other Anti-TNFs. In both countries, the adjusted IRR decreased slightly towards unity and the values for the adjusted estimates were marginally statistically significant in DK whereas it remained statistically insignificant in SE. In both DK and SE, GLM tended to be used during the study period as a second or even third line therapy. Thus GLM patients tended to have more severe disease and were at higher risk of colectomy. Due to the lack of covariates quantifying disease activity directly, disease activity can not be adequately adjusted for. In addition, the overlapping period was allocated to GLM therapy which could result in bias against GLM. Therefore, the finding of a small positive association with GLM exposure may reflect study bias and residual confounding by indication.

Although increased IRRs of all-cause TC was found for GLM therapy as compared to TP therapy, these IRRs should be interpreted with caution as the following potential sources of bias need to be considered. In clinical practice, GLM is used for patients with more advanced and severe disease than those treated with TP (i.e., confounding by indication). Many GLM patients were already previously treated with TP and with other biologics, while TP patients were naïve to both TP and biologics; thus they are not compatible. Accordingly, the finding may reflect differences in clinical profiles rather than a causal association.

Since no cases of HSTCL were reported, it was not possible to investigate this outcome further.

Collectively, this study provided no evidence that GLM poses an increased risk of CRC or all-cause TC.

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2 LIST OF ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	adalimumab
ATC	anatomical therapeutic chemical
AZA	azathioprine
CI	confidence interval
CD	Crohn's disease
CRC	colorectal cancer
DAG	directed acyclic graph
DK	Denmark
DVP	data validation plan
EMR	electronic medical record
GDPR	General Data Protection Regulation
GLM	golimumab
HSTCL	hepatosplenic T-cell lymphoma
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
IFX	infliximab
IR	incidence rate
IRR	incidence rate ratio
IV	intravenous
MAH	marketing authorization holder
M-H	Mantel-Haenszel
N.A.	not applicable
N.P.	not permissible
PASS	post-authorization safety study
PIN	personal identification number
PY	person-years
QBA	quantitative bias analysis
SAP	statistical analysis plan
SE	Sweden
TC	total colectomy
TNF	tumor necrosis factor
TP	thiopurine
UC	ulcerative colitis

Note: "register" and "registry" are synonymous terms that are used to refer to an official written record of names or events or transactions. In this protocol, "registry" will be used as a general term for such an entity, and "register" will be used when referring to a specific entity in which "register" is part of the official English translation of the name of that entity.

3 INVESTIGATORS

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Vendor/Collaborator	MedEngine DK ApS (formerly ApHER)
Investigators	See stand-alone document listed in Annex 1

4 OTHER RESPONSIBLE PARTIES

Not applicable (N.A.)

5 MILESTONES

Milestones related to study progress.

Milestone	Planned date	Actual date	Comments
Start of data collection			
End of data collection			
Registration in the EU PAS register			
Annual progress report 1			
Annual progress report 2			
Annual progress report 3			
Annual progress report 4			
Annual progress report 5			
Final report of study results, version 1.0		29 August 2023	
Updated final report of study results, version 2.0		13 May 2024	Corrected minor errors, which do not change the interpretation of results or overall study conclusion

Detailed milestones related to data and ethical approvals.

Detailed data milestones	SE	DK
Start of patient enrollment (start date for cohort entry)		
End of patient enrollment (end of cohort establishment)		
Start of follow-up[a]		
End of follow-up[a]		
Start of data extraction from registries by data owner / health data authorities		
End of data extraction (cut-off date)		
Latest registered outcome (data coverage):		
Patient registries		
Prescription registries		
Cancer registry		
Demographic data (deaths and migrations)		
Data released and made available for cleaning and analysis		

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

[redacted]

[a] The follow-up was one year without the enrollment of new patients, but with capture of outcomes and switches in therapies
[b] Data were recaptured twice after initial release and updated in the meantime
[c] Specific date cannot be given due to too few individuals (<5) at the latest date

Ethical approvals / Official decisions	SE	DK
Data Protection Agency	[redacted]	
Danish Health Data Authority		
Danish Health Data Authority Update		
Ethics Review Board (EPN Etikprövningsnämnden)		
Ethics Review Board Amendment		
Ethics Review Board Amendment		
Ethics Review Board Amendment		
Ethics Review Board Amendment		
National Board of Social Affairs and Health (Socialstyrelsen)		
National Board of Social Affairs and Health Update		
National Board of Social Affairs and Health Update		
National Board of Social Affairs and Health Update		
National Board of Social Affairs and Health Update		
National Board of Social Affairs and Health Update		
National Board of Social Affairs and Health Update		

6 RATIONALE AND BACKGROUND

SIMPONI® (golimumab [GLM]), a tumor necrosis factor (TNF) antagonist, was approved on 1 October 2009 in the European Union for the indications of rheumatoid arthritis, ankylosing spondylarthritis and psoriatic arthritis. On 19 September 2013, GLM received European marketing authorization for the treatment of moderately-to-severely active ulcerative colitis (UC). This registry-based study was established to provide additional information on colorectal cancer (CRC), colectomy, and hepatosplenic T-cell lymphoma (HSTCL), as outlined in the Risk Management Plan for SIMPONI® that was approved with authorization of the UC indication.

Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF antagonists, including GLM, to cause immune suppression affecting host defenses against infections and cancers. At the time of protocol writing, neither the pivotal registration trials evaluating GLM for the induction and maintenance of remission in patients with moderate to severe UC, nor any of the other clinical trials in the development program for GLM, had observed an association between GLM and CRC, HSTCL, or colectomy.[1,2] Use of data collected in population-based registries provides an additional source of safety data.

The study used data from nationwide health registries in Denmark (DK) and Sweden (SE). Because they are population-based, these registries were expected to capture all GLM therapy used for UC in these countries since the date of its market authorization. The national health registries in these countries also provide comprehensive, validated data on all dispensings of prescribed medicines, as well as interventions performed in hospital for diagnostic assessment and treatment, which were used to ascertain the study endpoints of relevance. Information from the national cancer registries was used to validate cases of CRC captured from hospital activity registrations. To provide context for interpreting the long-term safety data on UC patients treated with GLM, this study also followed similar patients with UC treated with alternative therapies for UC, including thiopurines (TP) and other TNF inhibitors.

Disease background. UC is a chronic inflammatory bowel disease (IBD) of unknown etiology characterized by inflammation primarily involving the colonic mucosa. The diagnosis of UC peaks between the ages of 15 and 35 years, but UC may affect all ages. The symptoms of UC depend on the extent and activity of the disease and may include bloody diarrhea and rectal bleeding, along with systemic symptoms of fever and weight loss. The clinical course is typically relapsing and remitting, although occasionally it may take an unremitting, continuous course. Anatomically, the inflammation in UC is uniform and continuous, with no intervening areas of normal mucosa. In nearly all cases, inflammation involves the rectum, and it extends proximally for a variable distance.[3]

Medical therapy. Medical treatment for UC depends on disease activity and extent. Patients with mild-to-moderate UC are treated initially with oral 5-aminosalicylic acid (5-ASA) medications combined with topical treatment with 5-ASA or steroid suppositories, plus 5-ASA enema or steroid foam preparations. The oral 5-ASA preparations should then be continued for maintenance of remission. For patients with moderate-to-severe UC, oral steroids are used to achieve initial disease control, followed by TP (6-mercaptopurine (6-MP) or azathioprine (AZA)) for maintenance in a step-up therapeutic strategy. At the time of writing this protocol,

the general situation was that for patients who do not respond to or are intolerant to TPs, the anti-TNF therapies infliximab (IFX), adalimumab (ADA) or GLM might be introduced. For patients hospitalized with acute severe disease or moderate-to-severe persistent UC, who have not responded to corticosteroids after five-to-seven days of treatment, therapeutic choices are either intravenous (IV) cyclosporine, an anti-TNF therapy or colectomy (systemic steroids are not recommended for use as long-term therapy in UC). Anti-TNF therapies are preferentially prescribed to patients with more severe, treatment-resistant disease. In addition to the general treatment scheme, when writing the protocol of this study, other therapies have shown activity against UC, including tacrolimus (a calcineurin inhibitor that is primarily used as an anti-rejection therapy in organ transplantation), tofacitinib (an oral Janus kinase inhibitor), and biologic therapies ustekinumab (anti-IL-12/23), natalizumab and vedolizumab (both anti-integrins).[3,4] Vedolizumab received European marketing authorization for the treatment of UC in 2014, tofacitinib in 2018, and ustekinumab in 2019. More recently, upadicitinib and ozanimod have received European marketing authorization for the treatment of UC.

Colectomy. When medical therapy fails, total colectomy (TC) is the surgical therapy of choice. The reported rates of colectomy in patients with UC vary widely depending on the activity and extent of the disease, clinical practice in different countries, and other factors. The 10-year cumulative colectomy rate ranged from 9% to 28% in population-based UC cohorts.[5,6] Risk for colectomy appears greatest in the first two years following diagnosis.[7] Since the introduction of anti-TNF therapies, there appears to be temporally decreasing rates of colectomy correlating with anti-TNF use in North America and Europe.[8] Anti-TNF therapies are used for moderate-to-severe UC and often as second or higher line therapies when other therapies fail. Accordingly, the risk for TC may depend on treatment history including short-term response to the TNF biologics, concomitant use of immunosuppressants, as well as treatment sequence. A recent retrospective cohort study that followed patients with UC reported that colectomy occurred in about 1.7%, 12%, and 19% of the patients treated with GLM as the first, second, and third anti-TNF therapy, respectively.[9] A similar study of UC patients commencing ADA also found a higher proportion (17.2%) of anti-TNF-experienced patients underwent colectomy than anti-TNF-naïve patients (2.9%).[10] The higher risk of colectomy observed in anti-TNF-experienced patients compared to anti-TNF-naïve patients may be associated with lower treatment response among patients who are more difficult to treat.[9]

The majority of total colectomies in UC are performed for intractable disease. Colectomy is also performed to treat CRC and depending on the clinical context, colorectal dysplasia. In a Norwegian population-based cohort study, CRC and dysplasia accounted for only about 10% of colectomies, while medically refractory UC accounted for 90% of the 49 colectomies.[7] Less common reasons for colectomy, which may be manifestations of intractable disease in UC, include emergent complications such as toxic megacolon, colonic perforation, massive hemorrhage and colonic obstruction.

Neoplasia. Compared to the general population, patients with UC are at an increased risk of CRC and colorectal dysplasia.[11] Colorectal dysplasia carries an increased probability of progression to CRC and may be treated with colectomy or managed through surveillance

colonoscopy.[12] Professional society guidelines suggest enhanced surveillance with colonoscopy to monitor for CRC and dysplasia in patients with longstanding UC.[3,4]

The 10-year cumulative risk of CRC in UC is approximately 2%.[13] The long-term cumulative probability of developing dysplasia or CRC was reported as 7.7% at 20 years and 15.8% at 30 years.[14] The risk of CRC varies within the UC population; risk factors for cancer in patients with UC include a long duration of disease regardless of clinical activity; extensive involvement of the colon; young age at onset of UC; severe persistent inflammation; the presence of primary sclerosing cholangitis; and a family history of CRC. More recent studies suggest that the risk of colonic neoplasia in UC has diminished over time.[15,16] A population-based study in the Danish UC population (1978-2008) found that the incidence rate (IR) of CRC was 1.05/1,000 person-years (PY).[16]

A separate nationwide register-based study in DK was conducted among patients with IBD from 1999-2012. This study found no association between anti-TNF therapy and CRC risk (adjusted relative risk 1.0 (0.48 – 2.08)).[17]

In addition to CRC, HSTCL (a rare lymphoma that is often fatal) has been identified as a possible risk in patients with IBD treated with anti-TNF therapies. Almost all patients who develop HSTCL have also been previously exposed to TPs, which may also contribute to the risk of HSTCL.[18]

7 RESEARCH QUESTION AND OBJECTIVES

This study addressed whether, in UC patients with similar baseline characteristics, the use of GLM is associated with the risk of CRC, all-cause TC, and HSTCL as compared with alternative therapies for moderate-to-severe UC. In this study, no prior research hypotheses were formulated.

Primary objectives

1. To characterize the clinical and demographic profile of first-time users of GLM in the treatment of UC, compared with the corresponding profile of first-time users of alternative therapies

2. To describe the risk of the following endpoints in patients exposed to GLM or exposed to alternative therapies

    2a. Incident CRC

    2b. Incident all-cause TC

3. If baseline characteristics suggest comparability, to estimate

    3a. The risk of incident CRC associated with GLM use relative to that associated with alternative therapies

    3b. The risk of incident all-cause TC associated with GLM use relative to that associated with alternative therapies

Exploratory objective

To describe the risk of incident HSTCL associated with exposures of interest

8 AMENDMENTS AND UPDATES

The initial study protocol was approved by EMA on 23 April 2015. All key changes made to the study protocol in subsequent amendments or updates are summarized in this table below. Amendments made as a consequence of such key changes are not listed.

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	05 Sep 2018	7.2, 8, 9, 9.2.2, 9.2.3, 9.3.2, 9.3.3, 9.3.4, 9.3.5, 9.4.1, 9.7, 9.7.3, 11	Amendment	To reflect changes and updates in background, objectives, study design, methods, cohorts, registry sources, outcomes, covariates, data analysis, and adverse event reporting
2	09 Mar 2022	6, Annex 1	Amendment	To reflect changes in milestones and dates of stand-alone documents
3	29 Jun 2022	3	Update	To reflect administrative changes
4	16 Nov 2022	4, 6	Amendment	To reflect changes in milestones

9 RESEARCH METHODS

9.1 Study design

This study was a long-term observational (non-interventional) post-authorization safety study (PASS) conducted in DK and SE to evaluate the treatment of UC with GLM and other approved UC therapies and assess the association between therapy exposure and the outcomes of interest (incident CRC, incident all-cause TC and incident HSTCL) in routine clinical practice settings. The study was based on a new user cohort design.

This was a secondary database study, based exclusively on registry data from automated central health registries in DK and SE (see Section 9.2). These registries comprise the entire UC population through information that is primarily collected for administrative reasons, such as reimbursement and organizational management, about inpatient care and outpatient care in emergency departments and hospital-based ambulatory specialty clinics. The registry data was collected prospectively, and data was analyzed retrospectively for this study.

Every patient who receives hospital-based care is identifiable by his/her unique personal identification number (PIN). Each hospital activity including all relevant diagnoses, surgical interventions and other therapies as well as procedures performed as part of diagnostic evaluation are registered. The PIN was used for the linkage of data and records between the nationwide health registries.

New epidemiological evidence suggests that currently in DK and SE combined, the prevalence of UC is approximately 100,000 patients[19]. From this population, three therapy cohorts were established based on first-time use of GLM, or first-time use of one of the two comparator therapies (anti-TNF other than GLM, or TP) from 19 September 2013 through 18 September 2020. Patients in the GLM cohort and comparator cohorts were characterized at baseline and followed from cohort entry until the end of the data collection period (the last date of follow-up was on 18 September 2021 in DK and on 31 December 2020 in SE, respectively) to determine the incidence of study outcomes (CRC, all-cause TC and HSTCL).

Throughout the study period, patients may have added, discontinued, or switched therapies. Accordingly, patients who develop outcomes may have been exposed to more than one therapy. Because of this, different definitions of exposure-risk windows were used for the CRC, HSTCL and colectomy outcomes risk analyses. For CRC and HSTCL outcomes, patients were assumed to be exposed forever after having commenced therapy, commonly referred to as “once exposed, always at risk”. For colectomy outcomes, the risk window for the association analysis ceased 90 days after therapy discontinuation but would be resumed if a patient restarted the same therapy subsequently. Additionally, entry into a new exposure cohort could be started for a new therapy.

As indicated in the protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 9.1), the automated register data are collected for administrative reasons. As a result, the register data may contain missing or incomplete information.

For further details about the DK and SE registers see protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 9.2.3).

9.2 Setting

Study base: Patients with UC and relevant therapy ascertained from the health registers

The identification of patients with UC in DK and SE was based on the centralized patient registration system for all inpatient and outpatient encounters registered with UC (International Classification of Diseases (ICD)-10 code K51.0-K51.9) as the primary discharge diagnosis. In operational terms, the date of diagnosis of UC was taken as the earliest date recorded in an encounter where UC had been recorded as the primary discharge diagnosis.

Therapy cohorts: Ulcerative colitis patients treated with GLM and alternative therapies

In DK and SE, patients with moderate-to-severe UC are managed exclusively by specialists with competence in gastroenterology in hospitals and hospital-based ambulatory clinics. Immunomodulatory and anti-TNF therapies are prescribed only in these settings. Registrations indicating initiation of therapies with anti-TNF therapies or TP (AZA or 6-MP) formed the basis for first-time inclusion in the therapy cohorts of interest (GLM cohort, Other Anti-TNF cohort and TP cohort).

Subsequently, patients may change therapy. For example, a patient initially commencing therapy with ADA may switch to first-time therapy with GLM and maybe even subsequently switch to IFX. In this example, the patient will have the first entry to the Other Anti-TNF cohort (due to initial therapy with ADA), then have a first entry to the GLM therapy cohort, followed by re-entry to the Other Anti-TNF cohort (due to the switch of therapy from GLM to IFX). In the analyses, the consequences of therapy switches in terms of exposure time and risk windows for the therapies of interest were managed as described in the statistical analysis plan (SAP), Section 6.3.4 (see also Section 9.9).

Registry sources

All health registries in the Nordic countries can be linked to each other through the unique PIN, assigned to each inhabitant within the respective countries, and used throughout the public sector. This unique setting permitted the establishment of the GLM therapy cohort and the comparator cohorts, as well as the long-term follow-up of all the study patients.

A comprehensive description of the Danish registries concerning their structure, organizational aspects and use for research purposes may be found in Thygesen *et al*. 2011[20] and on the homepage of the Danish National Board of Health. Link (in Danish): Danish National Board of Health. An overview of the Swedish national health registries is available on the homepage of the Swedish National Board of Health and Welfare. Link: Swedish National Board of Health and Welfare.

The health registries in DK and SE of relevance for the present study are listed in Text Table 1. Further details of each of the registries are described below.

Text Table 1. The central health registries of relevance for the present study.

Registry	Data collection period		Role in the study
	Denmark (DK)	Sweden (SE)	
Hospital activity registration systems (Patient Registries)	1977 (1995) - present[a]	1987 (2005) - present [a]	Identification of - Patients with UC - Extent of the disease - Prior hospitalizations - Therapies administered by hospital departments[b] - Procedures (lower endoscopies, and colectomies) - Occurrences of CRC and HSTCL - Emigration (only in SE)
Civil registration systems (only in DK)	1960 - present	N.A.	Deaths and other major vital demographic events, including emigration
Death cause registry (only in SE)	N.A.	2013 - present	Date of death
Prescription registries	1995 - present	2005 - present	Information on therapies by drugs purchased via prescriptions to patients with UC
Cancer registries	1943 - present	1958 - present	Validation of cases of CRC and HSTCL

[a] Years in parentheses indicate registration of outpatient activities
[b] In SE, the coding of administering therapies at hospital departments and clinics is incomplete. The Patient Registries are updated on an annual basis.

Patient registration systems

Denmark: The Danish National Patient Register contains data on all hospital activities in DK since 1977 (since 1995 for encounters on an outpatient basis) with coded diagnostic procedures and treatments together with administrative data.[20] Link (in Danish): Danish National Patient Register. Particularly concerning IBD and its components, Crohn's disease (CD) and UC, a study has verified that the validity of the UC diagnosis is more than 90% in the registry, increasing to more than 94% for the patients registered with specialized departments.[21]

The register is dynamic and updated, in practical terms, on a monthly basis, including amendments to previous registrations. The delay from an event to the public release of the corresponding data is in general about 2-3 months for encounters on an inpatient basis and in general longer for encounters on an outpatient basis.

Sweden: Starting from 1987, there is information on all completed in-patient admissions at publicly operated hospitals. Registration of encounters on an outpatient basis commenced in 2005. The key variables are diagnosis, surgery, external causes of injury (E-codes), gender, age, residence, hospital, specialty, and hospital admissions and discharges. The coding of therapies given to patients in hospitals or hospital-based outpatient clinics is incomplete but to an unknown extent. For the present study, this affected the identification of treatments with IFX since drugs administered by IV infusion were as a principle not identified from the prescription registration system.

Currently, the registry is updated annually with the release of data taking place in August/September, corresponding with a lag time of about 9-21 months. Link: National Patient Register.

Completeness of registrations of inpatient encounters is believed to be close to 100%.[22] Reporting from private outpatient clinics is incomplete, which causes an estimated overall deficit of 20% for outpatient encounters (Jacobsson A, Socialstyrelsen, Sweden, personal information). However, according to judgment from a clinical expert, activities for a disease like UC will, with very few exceptions, be managed in public clinics thus reducing reporting deficits to a minimum (Hertervig E, Skane University Hospital, Sweden, personal communication).

Civil registration systems

Denmark: The Danish Civil Registration System was established on a digitalized platform in 1968 and operates the allocation of PINs (and, from the PIN, information on age and gender) to all Danish citizens and stores information on births, moves (including migrations) and deaths in the Danish population.[20] Link (in Danish): Danish Civil Registration System.

Sweden: The digitalized civil registration system in SE is similar to the Danish system. Information on deaths in the study population can be obtained from the Swedish Cause of Death Registry. Link (in Swedish): Causes of Death Register.

Prescription registries

Denmark: The Danish National Prescription Registry contains data on all redemptions of prescriptions with information including person, date, location, prescribing doctor, package and strength and, thereby, numbers of defined daily dosages (DDD) purchased.[20] The registry is accessible for research purposes via Statistics Denmark and is updated continually, i.e. on a monthly basis. Link (in Danish): National Prescription Registry.

Sweden: The National Prescription Registry contains data on prescriptions redeemed in SE since 1999. The identity of the drug, prescribing doctor, amount, price and the date of prescription are registered in the database. From July 2005 the registry also contains data on the patient's PIN, gender, age and place of residence. The registry is updated monthly. Link: National Prescription Registry.

Cancer registries

There is a longstanding tradition for operating cancer registries of high quality in both DK and SE, and the content is accessible for research subject to relevant permissions. However, because of the time-consuming process of case validation, there is a substantial delay in the release of information from these registries. In this study, cases of CRC and HSTCL were ascertained primarily from diagnoses in the patient registration systems described above. For the final study report, cases of CRC and HSTCL in the inception cohorts were validated from the cancer registries. The registries are described in detail here:

Denmark: Since 1943 all cases of cancer have been reported to a nationwide registry, initially operated by the Danish Cancer Society. Since 2003, the Danish Cancer Registry has been operated by the Danish National Board of Health closely linked with the Danish National

Patient Register and supplemented with data from the Danish Pathology Register. The registry contains, in addition to the PIN, cancer diagnosis information (ICD-10 code system), date of diagnosis, information on location and morphology as well as data on the cancer stage.

The cancer registration system has a very high validity concerning the completeness of case registration as well as the validity of the data reported for the cases. It is however a disadvantage that there is a delay of up to two years before new information in the registry is published. See Engholm et al for a description of the Nordic cancer registries and their potential for epidemiological research.[23] Link (in Danish): Cancer Registry.

Sweden: Since 1958 all cases of cancer have been reported to a nationwide registry. Link: National Cancer Register. The registry contains, in addition to the PIN, cancer diagnosis information (ICD-10 code system), date of diagnosis, information on pathology and morphology as well as data on cancer stage and other clinical data. The cancer registration system has a very high validity concerning the completeness of case registration as well as the validity of the data reported for the cases. See Engholm et al for a description of the Nordic cancer registries and their potential for epidemiological research.[23]

9.3 Patients

Patients in this non-interventional study were required to meet the following selection criteria:

- The identification of patients with UC in DK and SE was based on a centralized patient registration system by all inpatient and outpatient encounters registered with UC as the primary activity diagnosis since the registers started until the data lock point. Extracted UC-codes were ICD-8: 56319, 56904, ICD-9: 556; ICD-10: K51%. The sign '%' indicates all underlying (lower level) codes. In DK, diagnosis is registered with ICD-8 codes until the end of 1993; afterward, the registration is according to ICD-10 codes. SE used ICD-9 codes between 1987 and 1996, afterward ICD-10 codes. Having UC registered at least once as the primary discharge diagnosis before or, at the latest, at the initiation of a first-ever UC therapy.
- Three UC therapy cohorts were constructed: GLM, Other Anti-TNF and TP. The first assignment to each of the three therapy cohorts was determined by the first-ever registered qualifying therapy from 19 September 2013 through 18 September 2020.
  - GLM cohort: The therapy cohort of UC patients treated with GLM was defined as all patients who were registered with GLM. The patients could receive TP and Other Anti-TNF therapies (IFX and ADA) before, during, or after GLM therapy.
  - Other Anti-TNF comparator cohort (IFX and ADA): The therapy cohort of UC patients treated with Other Anti-TNF was defined as all patients who were registered with IFX or ADA. The patients could receive TP and GLM before, during, or after Other Anti-TNF therapy.
  - TP comparator cohort: The therapy cohort of UC patients treated with TP was defined as all patients who were registered with a TP (AZA or 6-MP). The patients

must have been naïve to anti-TNF therapies (IFX, ADA and GLM) and vedolizumab.

- A patient could enter more than one cohort if the qualification criteria for entering another cohort were met after switching to another cohort defining therapy (see Section 9.4.1). For patients with their first cohort entry registered before 19 September 2020, the shift to alternative therapy cohorts was permissible after 18 September 2020.

- Patients were excluded if they were registered before cohort entry with a history of the following diagnoses.
  - HSTCL (ICD-10: *C861*), regardless whether a primary or a secondary diagnosis
  - CRC (ICD-8: *15300-15419,* ICD-9: *1530-1542,* ICD-10*: C18%, C19%, C20%*), regardless whether a primary or a secondary diagnosis
  - TC, regardless of cause (Nomesco classification code group: *JFH%*)
  - Colectomy other than total, regardless of cause (Nomesco classification code groups*: JFB2%, JFB3%, JFB4%, JFB5%, JFB6%, JFB9%*)
- Patients were also excluded if they had been dispensed etanercept (anatomical therapeutic chemical (ATC): *L04AB01,* therapy code: *B0HJ18A2* and *ML04AB01*) or certolizumab pegol (ATC*: L04AB05,* therapy code: *B0HJ18A5* and *ML04AB05*) before cohort entry. From a clinical perspective, the use of these therapies strongly suggests that the indication for the study-defining therapies was not UC.

Personal data for patients participating in this study were limited to those necessary to perform record linkages. The data were collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations in DK and SE. Additional information on the ethical conduct of this study is included in the protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 10).

9.4 Variables

9.4.1 Exposure

The main exposure of interest was therapy with GLM for UC. The GLM cohort was compared with cohorts of patients exposed to alternative therapies for moderate-to-severe UC: (1) Other Anti-TNF therapies (IFX or ADA) and (2) TP (AZA or 6-MP). During the follow-up period, UC patients who initiated GLM may have received or may have later received comparator therapies in various sequences. Similarly, patients who entered the study based on exposure to comparator therapies may have received or may have later received GLM.

- GLM cohort: The therapy cohort of UC patients exposed to GLM (GLM cohort) was defined as all patients who had at least one UC diagnosis and who after 18 September 2013 for the first time ever were registered as treated with GLM. The enrolment date was defined operationally as the date of initiation of GLM therapy. New members were added to the cohort with the last possible date of enrolment on 18 September 2020. UC patients with

antecedent diagnoses of CRC, colectomy, or HSTCL were not eligible for entry into the GLM cohort.

- Other Anti-TNF cohort: The therapy cohort of UC patients exposed to anti-TNF therapies other than GLM (Other Anti-TNF cohort) was defined as all patients who had at least one UC diagnosis and who after 18 September 2013 for the first time ever were registered as treated with IFX or ADA. The enrolment date was defined operationally as the date of initiation for this specific therapy. New members were added to the cohort with the last possible date of enrolment on 18 September 2020. UC patients with antecedent diagnoses of CRC, colectomy, or HSTCL were not eligible for entry into the Other Anti-TNF cohort.
- TP cohort: The therapy cohort of UC patients exposed to AZA or 6-MP (TP cohort) was defined as all patients who had at least one UC diagnosis and who after 18 September 2013 for the first time ever were registered as exposed to AZA or 6-MP. The enrolment date was defined operationally as the date of initiation for this specific therapy. New members were added to the cohort until the last possible date of enrolment on 18 September 2020. UC patients with antecedent diagnoses of CRC, colectomy (regardless of type and indication), or HSTCL were not eligible for entry into the TP cohort.

These definitions imply that only the first-time-ever exposure to GLM, Other Anti-TNF or TP registered between 19 September 2013 and 18 September 2020 qualified for the first entry to these cohorts. Registered use of a study medication prior to 19 September 2013 did not satisfy the criteria for entry into one of the therapy cohorts. A patient switching from Other Anti-TNF therapy to GLM (or vice versa) for the first time ever during the study period was, however, considered a new user of that second therapy, and could enter the therapy cohort of that second therapy.

No new patients were added to an initial therapy cohort entry from 19 September 2020 and onwards, but for the population of unique patients ascertained from 19 September 2013 through 18 September 2020, new therapy cohort entries were accounted for until the date of last date extraction or any other trigger for stopping follow-up, respectively.

Throughout this report, references are made to entries and memberships of the three therapy cohorts of relevance as well as patients' contributions to risk windows of relevant exposures. The terminology below will be applied.

The **initial therapy cohort** for a patient is the first cohort to which membership was qualified after the start of the study (19 September 2013). For each patient the initial therapy cohort was unique. The date of entering the initial therapy cohort was also the first date of observation for that individual.

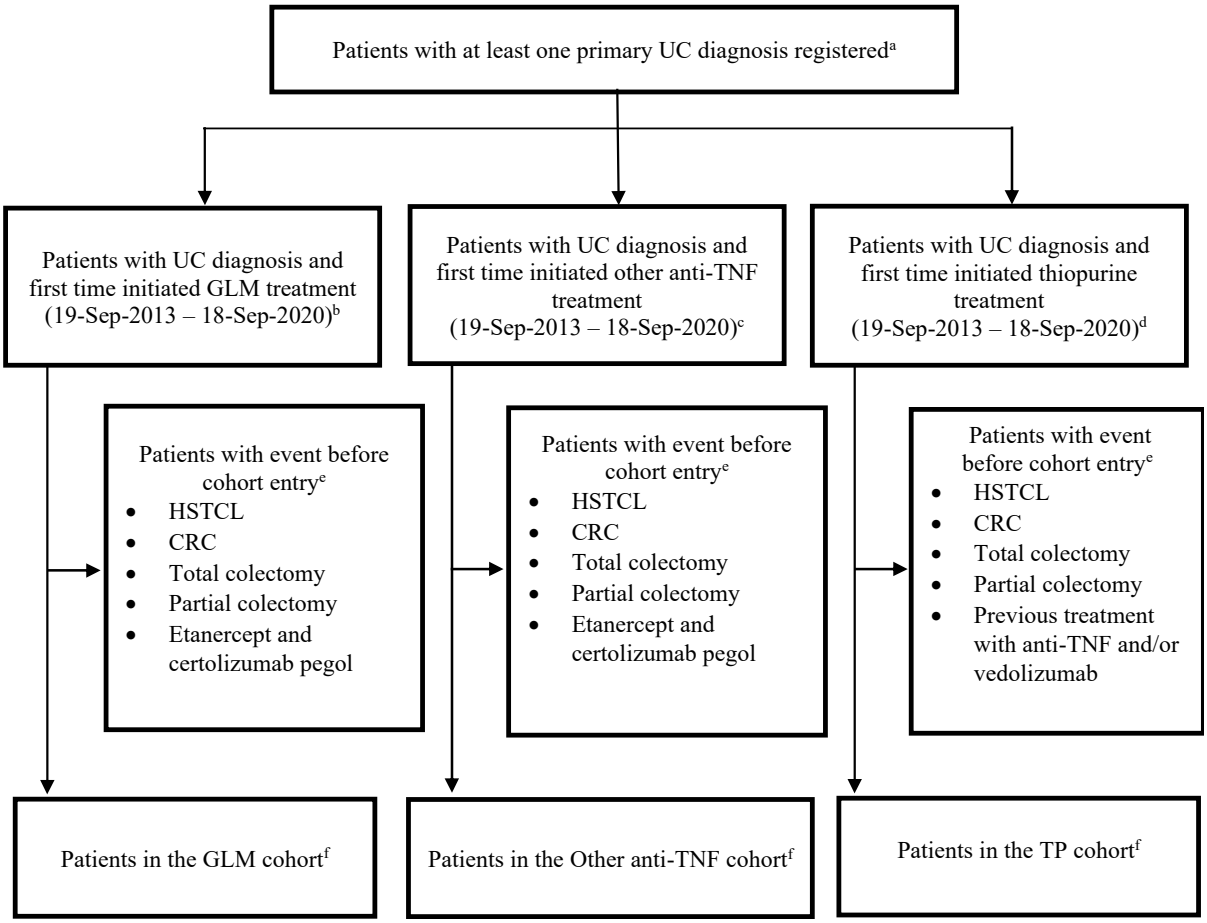
The **first entry to a therapy cohort** for a patient was the event of entering one of the three therapy cohorts (GLM, Other Anti-TNF, TP) for the first time. For a patient, the very first entry to a therapy cohort represented entry to the initial therapy cohort. A patient might subsequently have had a first entry to each of the other therapy cohorts or might even have experienced a re-entry to the same therapy cohort in case of re-commencing the therapy after a period with discontinued therapy. The first entry to a specific therapy cohort was unique for a given patient and was also the first date of observation for that specific therapy. However, a patient could be a member of more than one therapy cohort.

The term **risk window** was used to define amounts of person-time representing exposure to GLM, Other Anti-TNF and TP, respectively. Risk windows specific to therapy for a given patient were established as explained in Section 9.8.2, with aggregation of estimated duration of risk windows aggregated over all patients. Thus, a given patient could contribute to different risk windows during the study period but could only contribute to one risk window at a time.

The term **super cohort** was used to specify the unique patient population, regardless of membership of specific cohorts. Entry to the initial therapy cohort defined the first date of observation as member of the super cohort.

The establishment of the different therapy cohorts is illustrated in Text Figure 1. The study population included all individuals who were diagnosed with UC in DK or SE. If a patient had, for the first time registered, commenced therapy with any of the study therapies, between 19 September 2013 and 18 September 2020, the patient was allocated to the specific initial therapy cohort. As mentioned above, a patient could be allocated to other therapy cohorts subsequently. If a patient had experienced any of the events described in Text Figure 1 (*e.g.* CRC or colectomy regardless of type or reason for colectomy), before the initial cohort entry, the patient was excluded from the study.

Text Figure 1. Summary flow diagram of the establishment of therapy cohorts.



[a] Ascertainment was based on both inpatients and outpatient contacts registered in the history of national patient registers in DK and SE until the newest available data at the data lock point. The inclusion date of patients refers to the "admission date" for inpatient for hospitalized patients and the "date of first visit" for outpatient contacts.
UC must have been registered as the primary discharge diagnosis before or, at the latest, at the qualifying contact.
For all three therapy cohorts, the assignment to the therapy cohort was determined by the first qualifying therapy occasion after 18 September 2013 through 19 September 2020
[b] The therapy cohort of UC patients treated with GLM (the GLM cohort) was defined as all patients who for the first time were registered with GLM from 19 September 2013. The patients in the GLM cohort could be former users of the Other Anti-TNF therapies as well as TP. Last date of cohort entry: 18 September 2020
[c] The therapy cohort of UC patients treated with IFX or ADA (Other Anti-TNF cohort) was defined as all patients who for the first time were registered with IFX or ADA from 19 September 2013. Hence, ADA users must have been naïve to ADA and IFX users must have been naïve to IFX but ADA users may have used IFX before, and IFX may have used ADA before. The patients in the Other Anti-TNF cohort could be former users of GLM as well as TP. Last date of cohort entry: 18 September 2020
[d] The therapy cohort of TP patients (the TP cohort) was defined as all patients who for the first time were registered with TP (ATC: *L01BB02* or *L04AX01*). Users must have been naïve to both TP, any anti-TNF therapy and vedolizumab (ATC *L04AA33*). Last date of cohort entry: 18 September 2020
[e] A patient could have more than one event qualifying for exclusion and all such events were counted. The sum of events can therefore exceed the number of patients excluded
[f] A patient could enter more than one therapy cohort if qualification criteria for entering another therapy cohort were met after entering a specific cohort. The flow chart accounts for all therapy cohort entries which exceeds the number of unique patients represented in all therapy cohorts grouped together

Abbreviations and code specifications used for qualification to therapy cohorts (the sign '%' indicates all underlying (lower level) codes):
UC: Ulcerative colitis (ICD-8: *56319, 56904;* ICD-10*: K51%*)
GLM: Golimumab (ATC: *L04AB06*) Other Anti-TNF: Tumor Necrosis Factor Inhibitor other than GLM; therapies included are IFX (ATC: *L04AB02*) and ADA (ATC: *L04AB04*)
TP: Thiopurine therapy (ATC: *L01BB02, L04AX01*)
Naïvety to anti-TNF therapy: No history of therapy with anti-TNF therapies (ATC: *L04AB%*)

Abbreviations and codes specifications used for exclusion from entering therapy cohorts (the sign '%' indicates all underlying (lower level) codes):
HSTLC: Hepatosplenic T-cell lymphoma (ICD-10: *C861*). For exclusion, both primary and secondary diagnoses (in DK: A and B diagnoses, respectively) apply
CRC: Colorectal cancer (ICD-8: *15300-15419,* ICD-10: *C18%, C19%, C20%*). For exclusion, both primary and secondary diagnoses (in DK: A and B diagnoses, respectively) apply
Total colectomy: Nomesco classification codes: *KJFH%*
Partial colectomy: Nomesco classification codes: *KJFB2%*, *KJFB3%*, *KJFB4%*, *KJFB5%*, *KJFB6%*, *KJFB9%*
Etanercept (ATC: *L04AB01*) or certolizumab pegol (ATC: *L04AB05*)

Information about the use of anti-TNF therapies differs between SE and DK. In DK, these therapies are dispensed at the hospital departments managing patients with UC and were therefore not ascertainable from the prescription registry. Since the hospitals must register these therapies to obtain state refunds, therapies were captured through the procedure codes applicable to this class of therapies. In SE, the anti-TNF therapies GLM and ADA are ascertainable from the prescription registry through the ATC code. The ascertainment of IFX occurred both from the patient registration systems and the prescription registry. Information about hospital-based IFX use in SE was extracted from the patient registration system but the capture of therapies administered in the hospital setting was expected to be incomplete (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 9.2.3). Typically, pharmacy dispensing of IFX is not expected because it is administered as an IV infusion. However, some dispensing of IFX from pharmacies does occur, and it could be seen in the prescription register. Clinical consultants have indicated that this may occur when patients receive IFX infusions through private clinics. In summary, IFX use was ascertained through both the hospital and pharmacy registries, and it was expected to be incomplete in SE (addressed by sensitivity analysis in the study protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 9.7.3)).

Information on non-biologic therapy in UC was available from the prescription registries in both countries. The available prescription data included the date, strength and amount (in weight or volume) of the purchased drug. Using also the officially assigned defined daily dosages for the drug, the supply period (i.e. the duration of the prescribed therapy) was estimated. Neither the indication for prescribing the therapy nor the concrete daily dosage prescribed were available. PASS protocol, Annex 3 (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Annex 3) includes classification codes for study exposures.

9.4.2 Outcome

The *primary* outcomes were specified as follows:

Incident colorectal cancer: CRC was considered a relevant outcome if first diagnosed after cohort entry (a history of CRC disqualified patients for cohort entry). The date of diagnosis was defined as the date of referral for the first encounter where CRC was registered as a primary activity diagnosis in the patient registration systems. The outcome of CRC was validated against registrations in the cancer registries in DK and SE, respectively, at the end of the study, due to the delay in the release of updated information from these cancer registries. In DK, information on incident cases of CRC was available from the patient registration through 18 September 2021 and from the Danish Cancer Registry through 31 December 2020. In SE, information on incident cases of CRC was available from the patient registration system through 31 December 2020 and from the Swedish Cancer Registry through 31 December 2019 (see milestone tables in Section 5).

Incident all-cause TC: TC for ICD-10 codes were considered a relevant outcome if performed after cohort entry (a history of prior colectomy disqualified the patient for cohort entry). A study reported that among patients with IBD in an acute hospital setting, codes in the Danish NPR for TC had a positive predictive value (PPV) of 97% (156/161 confirmed; 95% confidence interval (CI): 93-99%), indicating they had high validity for purposes of this PASS.[21] No study has been identified describing the validity of TC ascertainment in the Swedish patient register. To address this question, the Sponsor performed a separate validation study that evaluated the validity of TC codes in SE, using a sample of electronic medical records (EMR) as the reference standard. The validation study concluded that the Swedish National Patient Register had a close to complete capture of all-cause TC.[24] The full validation study report is included as Annex 3.

The *exploratory* outcome was:

Incident hepatosplenic T-cell lymphoma: HSTCL was considered a relevant outcome if first diagnosed after cohort entry (a history of prior HSTCL disqualified for cohort entry). The date of diagnosis was defined as the date of referral for the first admission where HSTCL was registered as a primary activity diagnosis. The outcome of HSTCL was planned to be validated retrospectively against registrations in the cancer registries. Because the background incidence of HSTCL is so low (~1 case per million PY[25]), it was not likely that many outcomes would be observed during this study, and consequently, confidence limits around the parameter estimate would be wide.[25]

9.4.3 Covariates

Baseline patient characteristics and covariates were ascertained from automated registry data. Factors included age, gender, disease extent (following Montreal classification[26]), disease duration, history of UC treatments, hospitalization for UC, and selected comorbidities. Factors associated with CRC and with colectomy are described in Section 6.

The concept of "disease activity" factors into the risk of each outcome, but it is important to recognize that the term refers to two related but distinct concepts. First, as is commonly used in clinical practice, current disease activity refers to current biological colonic inflammatory activity, and it can be measured in several ways.[3,27] In clinical practice, it is commonly categorized into remission (no activity), or mildly/moderately/severely active UC, and

depending on the measurement scheme, the assessment may factor in stool frequency, rectal bleeding, vital signs (fever and pulse), laboratory findings (haemoglobin concentration and acute phase reactants), bowel endoscopic appearance, and patient and physician global assessments. Disease activity is dynamic; UC is characterized by flares, remission, and relapses. Disease activity is a major determinant in choice of UC therapy and is more closely associated with risk of colectomy for intractable disease. The second concept of disease activity refers to disease activity integrated over time, which can be conceptualized as "chronic inflammatory load", and is more closely associated with risk for advanced neoplasia.

In prospective clinical studies, acute disease activity is often measured using the Mayo Score, which reflects several clinical inputs that do not appear in automated data. However, according to clinical experts several clinically reasonable proxies can be found in automated data, including disease extent and evidence of a recent increase in UC-related healthcare utilization (*e.g.*, hospital encounters for UC and therapy modifications for UC). There is also no direct measurement of chronic inflammatory load in automated data or clinical records, but markers that have been used in prior research include disease duration, disease extent, and history of UC-specific therapies.[12,16,17,28]

Covariates are specified in the protocol and SAP (SAP, Section 6.3.4 and Section 6.6). All covariates from the protocol, with new additional covariates and modifications after consultations with clinical experts, are summarized in Text Table 2. Changes made after completing the SAP are explained below and in SAP, Annex 5.

Initially, hospitalization due to UC prior to cohort entry had also been considered as a proxy variable for disease activity. However, this variable has been excluded based on advice from clinical experts who did not consider hospitalization prior to therapy cohort entry, a proxy for disease activity. This approach has been supported by the detailed sub-analyses of hospitalizations prior to therapy cohort entry. EMA agreed with this conclusion described in the 5th annual progress report (submitted in June 2020).

According to the protocol and SAP, selected covariates (including age, specified comorbidities, disease duration, calendar time, prior colonoscopies and sigmoidoscopies, prior therapy episodes with steroids, prior TP therapy, and history of biologic therapies) should be updated at therapy cohort entry, i.e. switching to a new study therapy (SAP, Section 6.3.3, Table 3). Scrutiny of the real data revealed that only a limited number of patients switched to new therapies during the observation period of the study (see descriptive Tables D3.DK, D3.SE, D4.DK and D4.SE later in this report). Patients might have entry to the initial therapy cohort early in the study period or late, thereby having total observation time ranging from 105 days (for a Swedish patient entering the study on the latest possible day) to 8 years (for a Danish patient entering the study at the earliest possible date).

Under these circumstances, bias (misclassification) would be introduced when assigning covariate values to risk time if only done at switches in therapy. Thus, for a patient commencing and staying on therapy early in the study period, the time-varying covariates age and duration of UC would be kept constant at the values at baseline rather than reflecting the increase in age and duration of UC over several years. Furthermore, it would be ignored if the patient during the observation time experienced episodes of systemic therapy with steroid or frequent endoscopies that otherwise should be reflected in the covariates (see below). For

patients switching therapy, similar bias would be introduced during the observation time before switching. Overall, this would lead to covariate values that were systematically biased downwards, and the impact of this type of bias would vary between patients depending on whether they had entry to the initial therapy cohort early or late in the study period.

To reduce this bias and ensure appropriate assigning of covariate values to observation time the analysis team found it justified to change the scheme for updating covariates. For every patient, the status in the set of covariates was assessed on a daily basis throughout the observation time. Thus, the covariates representing categories by age, duration of disease and clinical variables (as described below) as well as switches in therapy were updated when a relevant change in the covariate took place.

Information on each of the covariates is provided below:

Country: Country of residence was classified as Danish or Swedish. This covariate was only used in the meta-analysis of aggregated data from DK and SE.

Sex: Sex was classified as males or females.

Age: Age was classified as a binary (<35 years versus ≥35 years) covariate due to lack of linearity between age and events and to obtain balanced strata without too small numbers.

Crohn's Disease (CD): CD was used in a sensitivity analysis to investigate the potential bias introduced by misclassification between CD and UC. See Annex 3: Classification codes, Section 1 of PASS protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022), Annex 3, Section 1). The variable was binary (No versus Yes to a history of CD) and was updated at the first registration of a relevant diagnosis.

Disease duration: Disease duration (using the date of first registered qualifying diagnosis of UC as the reference) was used as a proxy variable of chronic inflammatory. The disease duration was grouped in three categories (0-4 years; 5-9 years; ≥10 years) due to the lack of linearity between disease duration and events, and to obtain balanced strata without too small numbers.

Calendar year: Calendar year was originally supposed to reflect the time at entry to a therapy cohort as well as time at outcome. According to clinical experts, it should be expected that rates of CRC and all-cause TC as well as patterns of treatment over time, would change. This variable was classified as binary (≤2017 versus >2017) due to the lack of linearity between calendar year and events and to obtain balanced strata without too small numbers.

Extent of disease: According to the protocol, the extent of UC was categorised following the the Montreal classification[26] and measured as the maximal disease extent ever recorded for a given patient as an ICD-10 discharge diagnosis code as follows (see also Annex 3: Classification codes, Section 1 of PASS protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Annex 3, Section 1):

E1: Ulcerative proctitis	K51.2: Ulcerative proctitis
E2: Left sided UC (distal UC)	K51.3: Ulcerative proctosigmoiditis K51.5: Left sided colitis K51.5A Left sided proctocolitis (Danish variant) K51.5B Left sided hemicolitis (Danish variant)
E3: Extensive UC (pancolitis)	K51.0: Ulcerative pancolitis
Unclassifiable extent	K51: Ulcerative colitis K51.4: Inflammatory polyp K51.8: Other ulcerative colitis K51.8B: Ulcerative colitis with oral manifestations K51.9: Ulcerative colitis, unspecified

Colonoscopy and sigmoidoscopy: In UC, colonoscopy is used for diagnosis, and both colonoscopy and sigmoidoscopy are used for the evaluation of disease activity (flares), and as a screening tool for cancer. It is possible that the frequency of colonoscopy/sigmoidoscopy is a marker of chronic inflammatory load and possibly recent acute disease activity. However, it is not possible in the automated data to capture information on the reasons for performing an endoscopy. Clinical experts associated with this study have stressed that the validity of using the number of endoscopies as proxy variables for disease activity may be questioned. According to the protocol, the count of colonoscopies/sigmoidoscopies in one year preceding a therapy cohort was to be measured. This variable was grouped in three categories, according to the number of colonoscopies and/or sigmoidoscopies performed in the 12 preceding months (0, 1, ≥2 procedures registered).

Use of steroids prior to therapy cohort entry: The literature seems to suggest that those who require frequent corticosteroid courses within a 12-month period have more severe disease (steroid resistance) and need escalation of therapy[3]. According to the protocol, ≥2 courses of systemic steroids used in 12 months prior to therapy cohort entry should be included as a covariate. As it was not possible from the automated prescription data to define a course of systemic steroid treatment, an enumeration of prescriptions of systemic steroid during a period of 12 months was used. The number of registrations of prescriptions with systemic steroids within the preceding period of 12 months was summarized and categorized as a binary variable with the values 0: <2 prescriptions and 1: ≥2 prescriptions.

History of therapy with cyclosporine: This variable was exclusively used for describing the patient population according to history of more advanced therapy. The variable was measured as a binary variable (No/Yes to a history of cyclosporin therapy) with reference to the date of entry to the initial therapy cohort and the date of first entry to a therapy cohort.

History of colectomies other than TC: This variable was exclusively used in the sensitivity analyses to investigate the effect of possible misclassification of total colectomies. A history of colectomies other than total colectomies was positive at the first registration of a relevant

surgical procedure. See Annex 3: Classification codes, Section 3 of PASS protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Annex 3, Section 3) for specification of surgical codes).

Co-morbidities: Co-morbidities included primary sclerosing cholangitis representing a risk factor for CRC, as well as conditions for which anti-TNF therapy was also indicated, including rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis. See Annex 3: Classification codes, Section 1 of PASS protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Annex 3, Section 1) for specification of diagnosis codes). There were substantial differences between the different ICD code systems used in DK and SE during and before the observation period of the study. Because primary sclerosing cholangitis was not entered as a specific disease entity in the Swedish version of ICD-9, it was necessary to use the higher-level code (sclerosing cholangitis) as proxy. For the same reason, and due to small numbers, it was necessary to group joint diseases into one common co-morbidity reflecting arthropathies. The co-morbidity variables were updated at the first registration of a relevant diagnosis.

History of therapy with TP: This covariate was used as a proxy for indicating activity of UC, representing non-biologic immunomodulatory therapies. According to the protocol, the history of TP therapy was summarized as a binary covariate (Yes/No to a history of TP therapy) to be updated at therapy cohort entry, i.e. at switch of therapy. In this study, patients had to be naïve of exposure to TP at entry to the TP therapy cohort and therefore, this covariate was only used for adjustment in the primary analyses comparing GLM with Other Anti-TNF, but not when comparing GLM with TP.

History of therapy with biologics: According to the SAP, this covariate included therapies with monoclonal antibody-based anti-TNF study drugs (GLM, ADA, IFX) as well as other anti-TNF therapies (certolizumab pegol, etanercept) and vedolizumab. The covariate was used as a proxy for indicating activity of UC and intended to be operationalized as the number of new therapies accumulated at therapy cohort entry (grouped by three categories: 0, 1, ≥2). Since only very few patients experienced a cumulative history of more than two different biologic therapies, it was necessary to dichotomize the covariate as 'No' or 'Yes' to a positive history of prior biological therapy at initiation of biologic therapy. Accordingly, 'No' was used in case of no prior history of biological therapy at the initial entry to a biological therapy cohort, and 'Yes' was used in case of a at least one prior registration of a biological therapy at the initial entry to a biological therapy as well as for all subsequent switches to a new biological therapy.

Text Table 2. Tabulation of covariates summarizing initial and final parametrization

Covariate	Initial parametrization	Final parametrization	Comments
Country	DK: Denmark SE: Sweden	1: DK (Denmark) 2: SE (Sweden)	Only used for the meta-analyses based on aggregated data
Sex	Males Females	1: Males 2: Females	
Age	Continuous variable if linearity between age and outcome. Otherwise, categorical	1: <35 years 2: ≥35 years	Time-varying
Crohn's disease[a] (CD, ICD-10: K50.)	1: A history of CD registered 0: No history of CD registered	0: No 1: Yes	Used for sensitivity analyses concerning potential bias due to misclassification of CD and UC. Time-varying
Disease duration	Continuous variable if linearity between age and outcome. Otherwise, categorical variable with 4 categories (quartiles)	0: 0-4 years 5: 5-9 years 10: ≥10 years	Time-varying
Calendar year	Calendar year	1: ≤2017 2: >2017	Time-varying
Extent of UC	E1 (Ulcerative proctitis): K51 E2 (Left sided (distal) UC): K51.3; K51.5 E3 Extensive UC (pancolitis): K51.0 Unclassifiable extent: Remaining codes K51.	1: E1 Ulcerative proctitis 2: E2 Left sided (distal) UC 3: E3 Extensive UC (pancolitis) 9: Unclassifiable extent	Based on pilot studies: The ICD-10 code indicating maximal extent ever recorded was used
Colonoscopies, flexible sigmoidoscopies	Numbers of colonoscopies and flexible sigmoidoscopies within one year prior to cohort entry	0: No procedure registered 1: One procedure registered 2: ≥2 procedures registered	Time-varying
History of therapy with steroids	Courses of systemic steroid used in 12 months prior to cohort entry, ≥2 courses: yes/no	0: <2 prescriptions of systemic steroids 1: ≥2 prescriptions of systemic steroids	Time-varying
History of therapy with cyclosporine	1: Prior history of therapy 0: No prior therapy registered	0: No 1: Yes	For descriptive analyses only

History of colectomies other than TC	First registration of a surgical code representing other than TC (see Annex 3: Classification codes, Section 3 of PASS protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Annex 3, Section 3)	0: No 1: Yes	Used in sensitivity analyses only
Comorbidity[a]	Primary sclerosing cholangitis ICD-10: K83.0F	0: No to sclerosing cholangitis 1: Yes to sclerosing cholangitis	Time-varying
Comorbidity[a]	Psoriasis ICD-10: L40	0: No 1: Yes	Time-varying
Comorbidity[a]	Rheumatoid arthritis[b] ICD-10: M05.; M06	0: No 1: Yes	Time-varying
Comorbidity[a]	Psoriatic arthritis[b] ICD-10: M07.		
Comorbidity[a]	Ankylosing spondylitis[b] ICD-10: M45.		
History of therapy with TP[c]	1: Prior history of therapy 0: No prior therapy registered	1: ≥1 episode of treatment with TP registered 0: No episode of treatment with TP registered	Not used in comparisons between GLM and TP. Time-varying
History of therapy with biologics[c]	History of commenced therapies with biologics at entry to initial biological therapy cohort and at subsequent switches in biological therapy	1: No: No prior biological therapy at initial entry to a biological therapy cohort 2: Yes: Registration of at least one prior biological therapy at initial entry to a therapy cohort and at any subsequent switch to a new therapy.	Not used in comparisons between GLM and TP. Time-varying

Abbreviations used: CD: Crohn's Disease; CRC: colorectal cancer; ICD: International Disease Classification; TNF: tumor necrosis factor; TP: thiopurine; UC: ulcerative colitis

[a] Captured from primary or secondary discharge diagnoses

[b] Merged into one category containing arthropathies

[c] Including anti-TNF therapies regardless of being study therapies or not, as well as vedolizumab)

9.4.4 Operational definitions of variables

For all patients in the study population, the variables were extracted as shown in Text Tables 3A, 3B and 3C (one sub-table for each register). It should be noted that some variables may be available from several registers. For instance, in SE, migration status originates from the civil registration register and is exported to the patient register. This means that migration status was available in both the civil registration register and the patient register with no anticipated discrepancy between the two registers.

Cases of CRC and HSTCL were ascertained from the national cancer registries as well as via discharge diagnoses in patient registries in DK and SE. In DK, the ascertainment of cases of cancer in the cancer registry is coupled directly to the registration of cancer as a discharge diagnosis. Every time a cancer diagnosis is registered as a discharge diagnosis, an algorithm evaluates, based on all available data, whether the cancer diagnosis is incident for the patient or represents follow-up contacts with a prevalent cancer. The algorithm also determines the final coded information, including pathology diagnosis and cancer site, Therefore, the cancer registration in DK is considered virtually complete. In SE, however, it has been shown previously that there is an under-ascertainment of approximately 10% of cases of CRC in the Swedish Cancer Registry.[29] Furthermore, data from the cancer registries are published with significant delay and were not available for the last part of the study period: At the time of receiving the final versions of data extraction (28 October 2021 and 15 February 2022 for SE and DK, respectively), data on incident cases of CRC were available from the cancer registries through 31 December 2020. Data on cases of CRC and HSTCL were extracted from the respective cancer registries and were used for validation and sensitivity analyses for the part of the study period where data from the cancer registries were available as described in the SAP, Section 6.6.3. For both DK and SE, the validation analyses were based on the population of unique patients. Due to the small number of CRC/HSTCL outcomes, the part of the analyses that concerns the validation aspects were based on the cohort comprising all unique patients combined across all therapy cohorts.

In addition to the variables listed in Text Table 3A, data on emigration and death for patients were extracted from the relevant central registers in DK and SE, respectively (see Text Table 1). Follow-up for a patient ended at the date of observed event for each outcome or closure of the study, whichever came first.

Text Table 3A. Variables from the Danish and Swedish National Patient Registers.

Variable	Comment
PIN	Personal identification number
Sex	
Date of birth	
Date of admission	
Date of discharge	
Diagnosis*	Registered primary and secondary discharge diagnoses
Procedure code**	Surgery and examination
Date of procedure	
Pharmaceutical therapy	

*The following diagnoses were of interest: ICD-8: 563.01, 563.19, 569.04; ICD-9: 153,154A, 154B, 505B, 555A, 555C, 555X, 556, 575W, 576B, 576W; ICD-10: C18-20, C86.1, K50-51 and K83 (including subcategories). See also Annex 3: Classification of codes, Section 1 of PASS protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022)
**The following procedures were of interest: JFB2, JFB3, JFB4, JFB5, JFB6, JFB9, JFH, UJF32, UJF35, UJF42, UJF45, UJF82, UJF85, UJF92, UJG02 and UJG05 (including subcategories). See also Annex 3: Classification of codes, Section 3 of PASS protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022)

Text Table 3B. Variables from the Danish and Swedish National Prescription Registers.

Variable	Comment
PIN	Personal identification number
Sex	
Date of birth	
Date of redemption	
ATC*	
Pack size	Number of pills in each pack
Pack number	Number of packs
Strength	Strength of each pill

*The following ATC was of interest: A07, H02, L01, L04 (including subcategories). See also Annex 3: Classification of codes, Section 2 of PASS protocol (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022)

Text Table 3C. Variables from the Danish and Swedish National Cancer Registers.

Variable	Comment
PIN	Personal identification number
Sex	
Date of birth	
Date of diagnose	
Diagnosis (ICD)*	
SNOMED-O/3	
SNOMED-O/2-10	

*Diagnoses of relevance: C18-C20 (including subcategories), C86.1

9.5 Data sources and measurement

The principal data sources for this study, central nationwide health registries in DK and SE were based on automated data. Reference is made to the Section 9.2 concerning details about data sources, the reasons underlying the data sources chosen and how data linkage between data sources was used.

9.5.1 Study Procedures

The handling of data in the present study involved a series of steps, and required the submission of applications and approvals for access to data in DK and SE:

1. The Danish and Swedish national scientific coordinators submitted applications to the relevant authorities and agencies for permission to perform the study and to get access to data, including The Danish National Data Protection Board and the Danish National Board of Health and the Swedish National Board of Health and Welfare.
2. The Danish and Swedish national scientific coordinators established the national study populations and the ascertainment of all relevant events, after assembly of the therapy cohort of new users of GLM and the comparator cohorts. Each national scientific coordinator was responsible for acquiring and validating the datasets.

During the study period, annual progress study reports were produced, covering all study years except for the last year. Furthermore, two error reports were prepared. These reports reflected inconsistencies in the data analyses that were identified after the interim results had been submitted to the Sponsor and these two error reports are included in this final report (see Annex 4).

9.6 Bias

The data sources used in this study are the nationwide health registers in DK and SE, respectively. Even though those data sources are generally believed to be complete with a high level of validity of the data, there were several sources of potential bias of relevance for the study, including

- Diagnostic misclassification
- Lack of registrations of relevant therapies in prescription and/or patient registers
- Misclassification of outcomes
- Incomplete ascertainment of outcomes

Particularly in SE, there is an under-reporting of medical treatment administered by hospitals (as described in Section 11.2), and this particularly affects the capture of therapy with IFX because it is administered intravenously.

The extent to which these various sources of potential bias may have impacted the results is unknown. One of the purposes of the series of sensitivity analyses was to investigate such possible impact. Particularly for the issue of under-reporting of IFX therapies in the Swedish National Patient Register, a quantitative bias analysis (QBA) was performed. Further details are available in Section 9.9.4 and Text Table 5.

9.7 Study size

According to the study protocol, it was anticipated that for the GLM cohort a total of 500 patients and 1,250 PY would have been accrued during the first five years of the study (data from 2013-2018). The anticipated corresponding figures for the full period (cohort entries from 2013-2020) were 700 patients entering the GLM cohort and 2,450 PY accrued.

At the end of follow-up for this final report, a total of 893 patients had entered the GLM cohort, representing 3,287.1 PY. See also the Section 10.2 with descriptive analyses.

9.8 Data transformation

9.8.1 Data management: General views

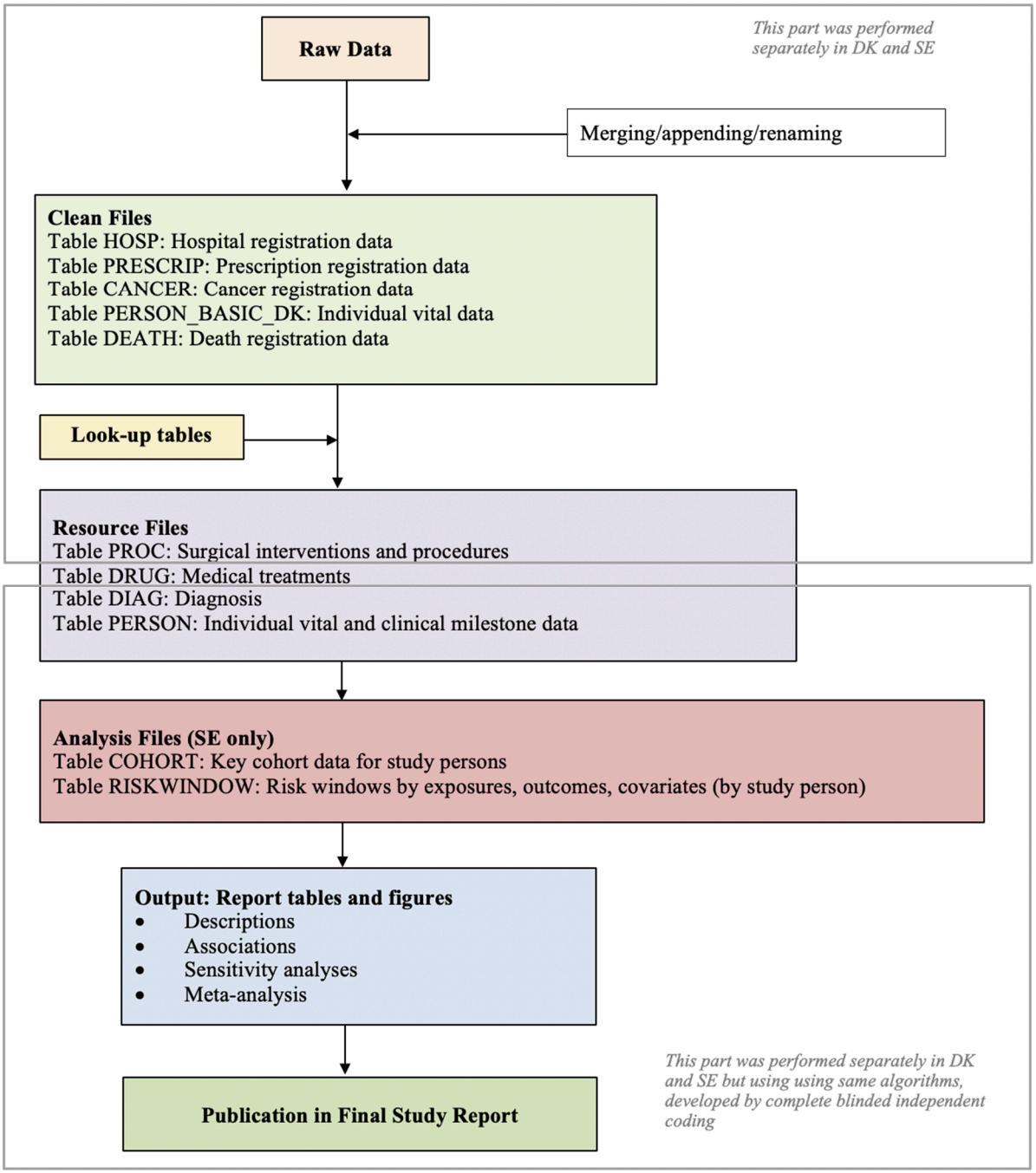
Data were managed at national level under the responsibility of the national coordinators in DK and SE, respectively, and according to the requirements and conditions defined by the health authorities in each of the respective countries. In accordance with the Data Validation Plan (DVP) (Stand-alone Document no. 7), it was important to ensure that the data management and the analysis followed the same plans and algorithms. Text Figure 2 shows the process from receiving the raw data to producing the final results, performed in parallel in SE and DK. The process included the following main phases:

- *Initial data preparation:* The steps from *raw data* to having established the *resource files*: QC level is medium, *i.e.*, independent review by another researcher.
- *Data analyses:* Steps including the *resource files* to produce the *analysis files* that form input to obtain the output *result tables and figures* as specified in the SAP. QC level is high, *i.e.*, with completely blinded independent double coding.
- *Publication of results:* The export of results to the Final Report for publication. QC level is high, *i.e.*, complete independent double-checking of the alignment of numbers in text sections with corresponding numbers in tables.

The extraction of data from DK was significantly delayed due to reorganization of the source register. The Danish data were released on 15 February 2022 and re-captured for technical reasons twice with completed data extraction on 19 March 2022. The data from SE were extracted on 23 September 2021 and released for initial scrutiny and preparation on 28 October 2021. The latest date with activities registered in the patient register in SE was 31 December 2020. In DK, the data coverage complied with the primary 7-years observation period plus the follow-up period from 19 September 2020 through 18 September 2021. In SE, the data coverage complied with the primary 7-years observation period but the subsequent follow-up

period was only from 19 September 2020 through 31 December 2020. (See Section 5 for further details).

Text Figure 2. Overview of initial management and preparation of data for the final analysis.



All data management and analyses were performed using SAS (DK data) and Stata (SE data). All data handling (including data management) was performed by two independent researchers experienced in register-based research. A reference is made to the DVP (Stand-alone Document no. 7) and SAP, Section 6.5.

9.8.2 Data management: Formation of risk windows

The principles of defining risk windows and thereby exposure to therapy are described in the PASS protocol, Section 9.3.5 (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 9.3.5) as well as in the SAP.

As the first step, the supply period for each registration of therapy was defined. This had to be done differently for therapies ascertained from prescriptions and for therapies ascertained from patient registration systems.

- Ascertainment of therapies from the national prescription registers: This concerned all TP therapies in both countries and some therapies with biologics in SE. The supply period was estimated from the amount of drug prescribed divided by the defined daily dosage officially assigned for the drug. For the TP drug 5-mercaptopurine, there is no officially defined daily dosage so the protocol specified a value of 50 mg.
- Ascertainment of therapies from the national patient registration systems: This concerned all therapies with biologics in DK and for most of the therapies with biologics in SE. For these therapies, neither information on amount nor duration of therapy were available. According to the protocol, a supply period of 90 days was assumed for GLM and ADA, and a supply period of 56 days for IFX.

A grace period of 30 days (arbitrarily defined and applied to all therapies) plus an extended risk period of 90 days (arbitrarily defined and applied to all therapies) was added to each supply period.

In the second step, all overlapping elements for same therapy (where the date of next registration was before the end of extended risk period from the previous registration of the same therapy) were collapsed into continuous blocks, starting with the first date of registration and ending with the date of the last extended risk window of the last registration. The corresponding risk window started, as specified in the protocol and in accordance with pharmacoepidemiological practice, with a gap of one day after the first registration date, and ended with the last date of the extended risk period that ended the block.

In the third step, the principles of incorporating risk windows as exposures in the primary association analyses were established differently depending on the outcome. For CRC and HSTCL the principle of ‘once exposed, - always exposed’ was applied, whereas for all-cause TC, 90-days extended risk window was applied. The principles used to form risk windows are outlined for each type of outcome below. Further details are contained in the Section 6.3.4 of the SAP.

For **CRC and HSTCL as the outcomes** (For HSTCL outcome, all principles below apply except without censoring all-cause TC):

Comparison between GLM and Other Anti-TNF:

- **GLM risk window** started one day after registered start of treatment and ended at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up; (6) One day after registered start of treatment with Other Anti-TNF study drug. In the latter case, GLM contributed to an overlap risk window together with Other Anti-TNF.
- **Other Anti-TNF risk window** started one day after registered start of treatment and ended at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up; (6) One day after registered start of treatment with GLM. In the latter case the Other Anti-TNF will contributed to an overlap risk window together with GLM.
- **Overlap risk window** was attributable to exposure for both GLM and Other Anti-TNF and started one day after registered start of treatment with a second anti-TNF study drug (ie. drug A = GLM followed by Other Anti-TNF = drug B, or drug A = Other Anti-TNF followed by GLM = drug B). The overlap risk window ended at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up. The overlap risk window was eventually allocated to GLM risk window.

Comparison between GLM and TP:

- **TP risk window** started one day after registered start of treatment and ended at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up; (6) One day after registered start of treatment with GLM or Other Anti-TNF study drug.
- **GLM risk window** started one day after registered start of treatment and ended at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up. In this comparison, subsequent treatments with Other Anti-TNF study drugs were not considered; accordingly, overlapping risk windows with Other Anti-TNF were attributable to GLM. In addition, if patients on TP registered GLM, subsequent overlapping person-times were attributable to GLM.

For **all-cause TC as the outcome:**

Comparison between GLM and Other Anti-TNF:

- **GLM risk window** started one day after registered start of treatment and ended 90 days after discontinuation *unless* one of the following events occurred before that. These events included: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up; (5) One day after registered start of treatment with Other Anti-TNF study drug. In the latter case, GLM exposure after the initiation of an Other Anti-TNF contributed to an overlap risk window together with Other Anti-TNF. Note that a given patient could contribute with more than one GLM risk window if the patient had more than one GLM treatment episode.

- **Other Anti-TNF risk window** started one day after registered start of treatment and ended 90 days after discontinuation *unless* one of the following events occurred before that. These events included: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up; (5) One day after registered start of treatment with GLM. In the latter case, Other Anti-TNF exposure after the initiation of GLM contributed to an overlap risk window together with GLM. Note that a given patient could contribute with more than one Other Anti-TNF risk window if the patient had more than one Other Anti-TNF treatment episode.
- **Overlap risk window** was attributable to exposure for both GLM and Other Anti-TNF and started one day after registered start of treatment with another anti-TNF study drug (ie. GLM followed by Other Anti-TNF, or Other Anti-TNF followed by GLM). The overlap risk window ended at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up; (5) End of 90 days after discontinuation of the first overlapping drug. Note that a given patient could contribute with more than one overlap risk window. It was originally planned that risk time with exposure for both GLM and Other Anti-TNF should be handled as a separate overlap category, but the overlap was eventually allocated to GLM risk window due to small number of outcomes.

Comparison between GLM and TP:

- **TP risk window** started one day after registered start of treatment and ended 90 days after discontinuation unless one of the following events occurred before that. These events included: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up; (5) One day after registered start of treatment with GLM or Other Anti-TNF. Note that a given patient could contribute with more than one TP risk window if the patient had more than one TP treatment episode without any anti-TNF treatments.
- **GLM risk window** started one day after registered start of treatment and ended 90 days after discontinuation unless one of the following events occurred before that. These events included: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up. In this comparison treatments with Other Anti-TNF study drugs were not considered; accordingly, overlapping risk windows with Other Anti-TNF were attributable to GLM. Also if patients on TP registered GLM, subsequent overlapping person-times were attributable to GLM. Note that a given patient could contribute with more than one GLM risk window if the patient had more than one GLM treatment episode.

While working with the real-life data, it became evident that therapy trajectories could be much more complicated than assumed in the protocol and SAP. For example, two alternative therapies might be registered to be commenced at the same date. Also, two alternative therapies might be administered simultaneously over longer periods of time. In such special cases, the code for handling risk windows and overlaps was modified and aligned during the quality control work (Section 9.10).

9.9 Statistical methods

9.9.1 Main summary measures

The health registers in DK and SE cover the same variables but there are important differences in data structure and reporting schemes across the countries. The countries differ with respect to permissions of using health data for research and how data access is regulated. Furthermore, as is the case with the under-ascertainment of therapy with IFX in SE, there may be different forms of bias which could impact comparability between the countries. Therefore, as per the protocol, data analyses were performed separately in DK and SE.

9.9.1.1 Descriptive analyses, including comparability of baseline characteristics

The analyses from DK and SE followed the same strategy plan and used identical table shells and outline of figures.

1. *Patient ascertainment.* The consecutive ascertainment of the study population was described, including attrition figures that indicate why potential patients did not qualify for the study. The distribution of number of patients enrolled in each of the three therapy cohorts (as defined in Section 9.4.1 and Text Figure 1) was enumerated for each calendar year, together with the cumulative total of follow-up time described in PY that accrued within each cohort.
2. *Baseline characteristics.* Demographic and clinical characteristics at initial study entry and at first therapy cohort entry were described for each cohort. Covariates included demographic and clinical characteristics, as described in Section 9.4.3. Analyses used standard descriptive statistics such as mean, standard deviation, median, interquartile range, and range for continuous variables. Number and proportions were presented for categorical variables. Based on insights from our clinical consultants, it was anticipated that the therapy cohorts would differ in terms of baseline characteristics. Therefore, the assessment of comparability of baseline characteristics at therapy cohort entry was performed and discussed in descriptive terms, *i.e.* without formal statistical testing of hypotheses.
3. *Therapy switches.* Within each therapy cohort, switches in therapy were identified and described by category of switch, according to the therapy cohorts outlined in SAP, Section 6.3.4. Among the covariates described in Section 9.4.3 potential determinants of switches were analysed descriptively.
4. *Descriptive analysis of incident CRC as outcome*
    a. The number of incident CRC was described for each therapy cohort, stratified by anti-TNF history (Text Table 4).
    b. IRs of CRC were calculated with 95% CIs. IRs were defined as the number of events divided by the PY at risk. It followed ‘once exposed, always at risk’ approach. Each patient contributed with PY from the time of entry to the therapy cohort regardless of any subsequent entries to other therapy cohorts (SAP, Figure 2).

c. Cumulative incidence of CRC was estimated by following the cohort comprising all unique patients from the first study entry without consideration of any assignment to therapy cohort and subsequent changes in therapy.

5. *Estimating IRs of HSTCL*. Since HSTCL was expected to occur very rarely, only descriptive IRs with Poisson-based 95% CIs were calculated according to the therapy cohort. No comparative analyses were conducted.
6. *Descriptive analysis of all-cause TC as outcome*

   a. The frequency of all-cause TC was described for each therapy cohort, stratified by anti-TNF history (Text Table 4).

   b. IRs of all-cause TC were calculated with Poisson-based 95% CIs. IRs were defined as the number of events divided by the PY at risk. In this analysis patients contributed with PY at risk from the first entry to the therapy cohort until the end of observation.

   c. The overall occurrence of all-cause TC was estimated as the cumulative incidence by following the members of the super cohort from the first study entry without consideration of any assignment to therapy and risk windows.

Text Table 4. Outline of exposure categories by defining therapy and history of relevant combinations of therapies at cohort entry.

Cohort defining therapy	Anti-TNF history	TP history
GLM	Anti-TNF naïve	Never, Prior and/or current
	Previous other anti-TNF	Never, Prior and/or current
Other Anti-TNF	Anti-TNF naïve	Never, Prior and/or current
	Previous other anti-TNF	Never, Prior and/or current
TP	Anti-TNF naïve	N.A.

9.9.1.2 Analyses of associations between exposures and outcomes

The main analyses assessed the associations between exposure to GLM and Other Anti-TNF therapies (the primary comparator group) with CRC as the outcome, and exposure to GLM and TP with CRC as the outcome. Similar analyses were performed with all-cause TC as the outcome. In addition to the crude association measures, estimates were obtained in models with adjustment for those covariates judged relevant in the directed acyclic graph (DAG) process (as described below) as well as models with the full set of covariates (See Text Table 2 and Text Table 7).

According to the protocol, Cox proportional hazard regression should have been applied in the primary association analyses. Inspection of log-log plot (−log(−log(S(t))) against log(t) (see

Section 10.4) showed that the assumption underlying using Cox proportional hazard regression was not fulfilled for analyses in both DK and SE. Due to masking rules it was not permitted to show the plots. In accordance with the protocol and SAP, the association analyses were performed using Poisson regression of number of events with the logarithmic transformation of person-time as offset (also called piece-wise exponential model). Incidence rate ratios (IRRs) were used to estimate the relative risk with corresponding 95% CIs.

Analyses with CRC as the outcome: The associations were analysed under the general underlying principle 'Once exposed, always at risk' (see SAP, Section 6.3.4 and Figure 2 for further details and illustrations). Time since cohort entry was stratified by sex, age group and calendar year. Combinations of exposures to therapies were analyzed as time-dependent variables, following risk windows described in Section 9.8.2.

Analyses with all-cause TC as the outcome: As described in Section 9.8.2, for attribution of all-cause TC, 90-days risk window extension was used. For this analysis, only those all-cause TC events that occurred from therapy cohort entry to 90-days after discontinuation of the therapy were included; events that occurred outside that risk window were excluded from the analysis. If the patient restarted the same cohort defining therapy after 90 days, then follow-up continued from one day after restart and extended through 90 days after the end of therapy exposure or until one of the general triggers for end of follow-up occured, whichever came first. All-cause TC events and follow-up person-time during the gap period between the two therapy episodes were not included in the analysis.

Potential effect modification by time period immediately following a switch in therapy (for colectomy outcome) was examined in a sensitivity analysis.

Confounding: UC is a chronic disease, and over time therapies and the course of disease may change. As noted in Section 6, the choice of medical therapy for UC depends on disease activity and extent. At the same time, these characteristics were also risk factors for the study outcomes, CRC and all-cause TC. Therefore, the results were at risk of confounding by indication.

A special case of confounding related to the comparison of outcomes in the TP cohort with those in the anti-TNF cohorts that included patients in whom therapy with TP has failed. In clinical practice, TPs typically are administered to patients with mild disease before anti-TNF therapies, implying that patients commencing therapy with anti-TNFs are not comparable with patients commencing therapy with TPs in terms of the effects of previous therapies. Thus, this caveat when comparing GLM cohort with TP cohort was addressed in a sensitivity analysis where outcome rates in the TP cohort were contrasted with the corresponding outcome rates in the GLM cohort naïve to TP.

Covariates and their updating are specified in Section 9.4.3 and Text Table 2. The set of covariates was based on consultations with clinical experts and the literature.

Confounders to be included in the multivariable analysis (adjusted model) were identified using the DAG method (the details of DAG are presented in SAP, Annex 4). Initially, all covariates (including explanatory variables and potential confounders) were entered into a DAG. In the DAG, all covariates were placed according to their possible role in causal

pathways from exposure to outcome. Based on the DAG, a minimal sufficient adjustment set of confounders was identified to be included in the multivariable analysis.

Three models were applied to examine the association between therapies and the two respective outcomes (incident CRC, and all-cause TC).

Model 1: An unadjusted model.

Model 2: A model adjusted for the confounders in the minimal sufficient adjustment set (i.e., DAG adjusted).

Model 3: Model 2 further adjusted for the confounders not included in the minimal sufficient adjustment set but included in SAP, Table 3 (i.e., fully adjusted).

When establishing the final multivariable model, it was checked that (1) convergence was obtained for each model; and (2) none of the standard errors of the parameter estimates were very large compared to the parameter estimates (such as 100 times larger); even if convergence was obtained, this situation would indicate problems with the analysis. Covariates exhibiting problems of these kinds were excluded to ensure that the statistical multivariable model, eventually selected, provided clinically interpretable results.

It had been considered to develop a composite score to indicate disease activity prior to a therapy cohort entry based on the proxy variables (colonoscopies, flexible sigmoidoscopies; history of therapy with steroids; history of therapy with TP; history of therapy with biologics, see Text Table 2 Tabulation of covariates). However, it was judged that the proxy variables could be handled individually in the analysis. Initially, a univariable analysis was used. Next, a multivariable analysis was performed including covariates (various proxy variables). Exclusion of proxy variables for disease activity followed the guidelines described above.

9.9.2 Main statistical methods

According to the protocol Cox proportional hazard regression should be used for the primary association analyses, using Poisson regression model as the alternative in case the assumption underlying using Cox proportional hazard regression was not fulfilled (based on inspection of the so-called log-log plot (−log(−log(S(t))) against log(t)) for each group in the analysis). Since the assumption about proportional hazard functions was not fulfilled (see Section 10.4) for all analyses, the association analyses were performed using Poisson regression of number of events with the logarithmic transformation of person-time as offset (also called piece-wise exponential model). Exposure-specific risk windows were established as described in Section 9.8.2, applying a 90-days extended risk window for all-cause TC as the outcome. For every level of each covariate, IRs were estimated as the number of outcomes divided by the corresponding person-time at risk aggregated over exposure categories and IRR were used to estimate relative risk. Corresponding 95% CIs were estimated for IRs as well as for IRRs.

All statistical analyses were performed using the software packages Stata (version 17) (https://www.stata.com) and SAS (https://www.sas.com/en_us/software/stat.html) with the exception of the meta-analysis of aggregated data from DK and SE. The meta-analysis used the R package as described under point 4 below. Data handling (including analyses) was performed by two independent researchers experienced in register-based research.

The statistical analysis addressed each of the study objectives based on a conceptual framework for exposures and outcomes described above. Basic descriptive tabulations and the statistical analyses were performed at national level in DK and SE separately. Data analysis had to be performed in the server environment chosen by the data provider due to legal data protection requirements. The choice of software used for the statistical analysis was thus determined by the data provider and was supported by reproducible data management procedures with full documentation of scripts and algorithms.

The data analysis consisted of four parts:

1. Descriptive analyses, including
    a. A description of the accrual of person-time from the date of first entry to a therapy cohort based on the distribution of patients as accounted for in the SAP, Figure D2. The numbers of entries are not additive across therapy cohorts because a patient may enter more than one therapy cohort, and therefore the cohorts are not mutually exclusive.
    b. Characterizing and comparing the clinical and demographic profile at entry to the initial therapy cohort. Patients were only included once in the initial therapy cohort. Second, clinical and demographic characteristics were presented at first entry to a therapy cohort for comparisons across cohorts. In the latter approach, patients might be included more than once pending switches in therapy. No tests were performed.
    c. Describing the IRs of CRC, all-cause TC and HSTCL by therapy cohorts (as treated approach). For all-cause TC, total person-time was used without applying a 90-days extended risk window.
    d. Describing the cumulative risk of incident CRC and all-cause TC in the super cohort of unique patients.
2. Analyses of associations between exposures and outcomes, including
    a. The IR of CRC associated with GLM *relative to* that associated with alternative therapies.
    b. The IR of all-cause TC associated with GLM use *relative to* that associated with alternative therapies.
3. Analyses to investigate sensitivity and validity aspects
    a. Alternative rules for establishing exposures and risk windows
    b. Re-specification of patient profiles
    c. Re-specification of outcomes
    d. Re-specification of covariates
    e. Ascertainment of incident cases of CRC from cancer registries (SE only)
    f. QBA of under-ascertainment of IFX in SE

4. A meta-analysis of aggregated data from DK and SE to obtain weighted combined estimates of measures of association and to investigate potential heterogeneity in the results.

A meta-analysis was completed to combine the effect estimates from the two separate studies conducted in SE and DK, which utilized the same protocol and operational definitions for exposure, outcomes, and covariates, and with aligned analysis methods. The aim of the meta-analysis was to obtain a weighted combined estimate of the association measure across the studies involved and to investigate the potential heterogeneity across studies. To accomplish this, the aggregated data from each country-specific analysis was required to be exported into a common analysis environment. With compliance to General Data Protection Regulation (GDPR) guidelines, small patient sample size limited the number of stratifications and subgroups that could be examined in this meta-analysis.

The protocol specified the application of Mantel-Haenszel (M-H) methodology with a quantitative assessment of heterogeneity between the results from DK and SE. However, it was not possible to identify a software that could apply M-H analysis to aggregated person-time data at the same time as providing a quantitative assessment of heterogeneity and offering the inclusion of covariates in the analysis. Because compliance to GDPR guidelines was prohibitive for the inclusion of more than one covariate anyway, it was prioritized to use software that could perform a M-H analysis for aggregated person-time data together with a quantitative assessment of heterogeneity. Such an analysis was not possible in neither of the two statistical packages used for this study (SAS in DK and Stata in SE). As the alternative, the function rma.mh in the package metafor included in the R package was used (https://www.rdocumentation.org/packages/metafor/versions/3.0-2/topics/rma.mh). This program offers estimation of I^2 as a measure of heterogeneity, together with the corresponding test statistics, in addition to the weighted combined IRR-estimates (but without adjustment for covariates).

9.9.3 Missing values

Missing values were handled as part of the sensitivity analyses (Text Table 5) or as reviewed in SAP, Annex 5.

9.9.4 Sensitivity and validation analyses

Several sensitivity analyses were performed to examine the robustness of results to alternate specifications of the study population, risk window, outcome definitions, competing risk, and additional adjustment using QBA to account for incomplete ascertainment of prior therapy with IFX in SE (SAP, Annex 2).

A range of sensitivity analyses (Text Table 5) were performed to cover the issues listed below:

Alternative inclusion criteria for patients with UC. The comparative analyses were rerun on subsets of the original study population (1) excluding patients who ever had a registered

diagnosis of CD and (2) limited to patients who had at least 2 independent episodes where UC was registered as the primary diagnoses by the time of cohort entry.

Alternative specifications of the risk window for incident CRC as outcome. The comparative analyses were rerun using the alternative definitions of the risk windows for CRC, as stated in the SAP, Section 6.3.4.

Because the actual biologic risk window for neoplastic risk is not known, alternative definitions of the risk window that lag the start of time at risk and vary the potential period at risk after exposure discontinuation were evaluated:

- Alternative scenario 1: For all study exposures, the risk window begins 6 months after start of current exposure and ends 6 months after exposure discontinuation;
- Alternative scenario 2: For all study exposures, the risk window begins 6 months after start of current exposure and ends 2 years after exposure discontinuation

Alternative specifications of the risk window for all-cause TC as outcome.

- In a sensitivity analysis, an alternative risk window extending to 6 months after the last therapy, or until one of the censoring events for end of follow-up occurs, whichever came first, was used.
- Because the therapeutic effect of TPs is not expected until approximately 3 months after initiation of therapy, in any comparison of GLM with TPs for all-cause TC, the alternative risk window for TPs started 90 days after the start of therapy and ended 90 days after the last therapy, or until one of the censoring events for end of follow-up occured, whichever came first.
- In another sensitivity analysis, all follow-up time (*vs* 90-days risk window) that currently had been used in the progress reports was conducted in the final analysis.

Imputing classification of maximal extent of UC for patients where data were missing. Patients without a registration of maximal extent of disease were assigned minimal extent (E1, see SAP, Section 6.3.4) and maximal extent (E3, see SAP, Section 6.3.4), respectively, to assess the robustness of using extent of disease as a covariate.

Alternative definition of the "all-cause TC" outcome. Instead of using the all-cause TC definition, the main comparative analyses were repeated to estimate the comparative risk of "colectomy for intractable disease". Although the indication for performing a colectomy was not available in the hospital activity registration system or other sources of automated data, the alternative outcome could be estimated using the following clinical logic. A colectomy performed during hospitalization where the principal activity diagnosis was CRC (ICD-10 codes C18. – C20.) was considered as surgery to treat CRC. All other total colectomies were assumed performed for intractable disease.

Another sensitivity analysis was conducted using any colectomy (regardless of type and indication, *i.e.* all total and partial colectomies are included) as the outcome.

Distortion of risk estimates because of competing risks.

Competing risks were defined as: During the clinical course of UC, the risk of developing CRC will compete with the risk of having a colectomy, and vice versa. Colectomy precludes (at least in theory) subsequent risk for CRC, and CRC likely leads to therapy by colectomy, which at least to some extent, may preclude the risk of subsequent all-cause TC.

Two approaches were used to assess the impact of competing risk.

- First, the analyses were repeated using censoring criteria modified from the primary analysis. For the outcome of CRC, the risk was estimated *without* censoring at the "all-cause TC" event. For the outcome of "all-cause TC", the risk was estimated *with* censoring at the CRC event.
- The second approach to address competing risk involved a sensitivity analysis that described cumulative event-free incidence of survival, using a composite definition of outcome that included the occurrence of one or more events of CRC, all-cause TC, or death.

Managing new therapies. New biologic therapies (including vedolizumab) were approved with UC as an indication after 13 September 2013, when the study period began. SAP, Section 6.3.3 explains how such therapies were managed in the analysis.

Managing registration of therapies with incomplete ('high level') therapy codes. Therapy episodes in the Danish patient register may occasionally be registered with unspecific codes ('high level' codes) that specify the category of therapy but without having the details about the specific therapy. To the extent such codes are used, commencement of new therapy and switches between therapies may be misclassified. Based on pilot studies it was anticipated that the use of unspecific codes is limited. The impact of such potential misclassification was assessed in a sensitivity analysis where all patients with at least one unspecific code registered as therapy of relevance for UC were excluded.

Distortion of risk estimates because of misclassification of all-cause TC in SE. The separate validation study reported by IQVIA (see Annex 3) indicated that Swedish National Patient Register has a close to complete capture of TC, and the TC outcome identified from the registry is highly valid. There is no reason to believe there is a differential misclassification of all-cause TC across cohorts. Thus, there was no need for further bias analysis for all-cause TC as the outcome.

Managing colectomies occurring outside a risk window. As a starting point, all-cause TC events occurring within risk windows were counted as outcomes. Colectomies occurring in risk windows without exposure were excluded from the primary analysis. In a sensitivity analysis performed to assess the effect of ignoring colectomies occurring outside risk windows, the IR for the all-cause TC outcome occurring outside the risk windows was estimated using PY outside the risk windows as denominator values (i.e., numerator and denominator used the same time period to identify the colectomy event and to calculate PY).

Validation of CRC and HSTCL as outcomes. Because validation of outcomes needed to be conducted in the population of unique patients and also due to small number of CRC/HSTCL outcomes, the analyses were done in a super cohort, that is, a combined therapy cohort. This super cohort was not stratified by therapy cohort for both the SE and DK data sets.

- In SE: For the final data analysis, data from the cancer registry were available for the study period until the end of 2020. The analysis of completeness of ascertainment in the cancer registry was performed using identification from hospital discharge diagnoses in a conventional capture-recapture technique[30] supplemented with kappa-statistics. In addition, agreement with date of diagnosis was explored on a descriptive basis. A sensitivity analysis was performed, analyzing associations between exposures and cancers as outcomes based on the CRC cases ascertained from the Swedish Cancer Registry only, regardless of whether or not the cases were ascertained by hospital discharge diagnoses.
- In DK: For the final data analysis, data were available from the cancer registry for the study period until the end of 2020. In DK, reporting of cancers to the Danish Cancer Registry is linked to the reporting of activities and discharge diagnoses to the National Patient Register.[31] Because of the strong correlation between the Danish Cancer Registry and the Danish National Patient Register, it was not possible to apply conventional capture-recapture methodology to assess the completeness of ascertainment of the respective data sources. Thus, this assessment was done on a purely descriptive basis only. A sensitivity analysis was performed, analyzing associations between exposures and cancers as outcomes based on the CRC cases ascertained from the Danish Cancer Registry only, regardless of whether or not the cases were ascertained from hospital discharge diagnoses.

Distortion of risk estimates because of residual confounding in SE. In this study, IFX use was a part of exposure (one component of Other Anti-TNF cohort), but history of prior IFX use was also a potential confounder for the association between GLM exposure and study outcomes. Studies have shown that patients initiating GLM or ADA who have previously received biologic therapy have a higher risk of all-cause TC than those who are naïve to biologic therapies.[9,10] IFX is systematically under-ascertained using Swedish registry data, and if history of its use differs between GLM and ADA initiators, confounding would be likely.

A QBA was conducted using the method published by Lash *et al*.[32,33], to adjust for bias due to severe under-ascertainment of prior IFX exposure in SE. The observed point estimate of IRR_{obs} from the main study was adjusted using bias parameters that were estimated from additional data sources (see Annex 3). In contrast to the primary analysis, where the comparison was GLM vs Other Anti-TNF (including IFX and ADA), in the QBA comparative analysis in SE for the outcome of all-cause TC, the comparison was GLM *vs* ADA exposures and IFX was adjusted as an unmeasured confounder. The details of the QBA are presented in SAP, Annex 2.

Text Table 5. Overview of sensitivity analyses.

Domaine (with reference to specific sensitivity analysis)	Description of sensitivity analysis
Switches in therapy and overlapping risk windows for all-cause TC **Table S1A** **Table S1B** **Table S1C**	1. Overlapping risk was attributed to GLM in the analysis stratified for prior use of biologics. 2. Overlapping risk time was attributed to old therapy only. 3.Applying a 90-days lag period for all new therapy starts regardless of therapy switches.
Misclassification of UC diagnosis: Admixture of patients with Crohn's Disease (CD) Patients with a false-positive diagnosis of UC **Table S2**	The primary analysis included patients with a diagnosis of CD prior to cohort entry as well as patients with only one UC diagnosis registered (reflecting a possible false-positive case). In this sensitivity analysis the study population was restricted to patients with (a) two independent episodes where UC was registered as the primary discharge diagnosis; and (b) never having CD registered as primary discharge diagnosis.
Misclassification of exposure due to the use of high level therapy codes (DK only) **Table S3**	Excluding patients with one or more high level therapy code registered during the observation period.
Risk window for attribution of CRC **Table S4** **Table S5A** **Table S5B**	1. For the TP cohort, person-time accrued one day after initiation of TP until end of follow-up regardless of therapy discontinuation. However, if patients switched from TP to an anti-TNF therapy, subsequent PY and events attributed to anti-TNF cohort only after switching in the primary analysis. In the sensitivity analysis, if patients switched from TP to an anti-TNF therapy, subsequent PY and events were attributed to both TP and anti-TNF groups. 2A. For all cohorts, risk window started 6 months after first exposure and ended 6 months after exposure discontinuation. 2B. For all cohorts, risk window started 6 months after first exposure and ended 2 years after exposure discontinuation (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 9.3.5).
Censoring for all-cause TC for attribution of CRC **Table S6**	In the primary analysis all-cause TC was considered a censoring event in the assessment of risk of CRC. A sensitivity analysis considered any type of colectomy as a censoring event.
Risk windows for attribution of all-cause TC **Table S7A, Table S7B, Table S7C**	1. For all cohorts, risk window started one day after first exposure and ended at 6 months after last therapy or until one of the general triggers for end of follow-up (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 9.3.5). 2. For the TP cohort, risk window started 90 days after first exposure and ended 90 days after the last therapy or until one of the general triggers for end of follow-up (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 9.3.5). 3. The analysis of using all follow up time after entry of therapy cohorts (*vs* 90-days risk window) that had been used in the progress reports was conducted in the final analysis as a sensitivity analysis.
Competing risks for attribution of CRC **Table S8** **Figure S1** **Table S9**	1. There was no censoring at the date of first all-cause TC registered. 2. Analyses were supplemented with estimation of cumulative survival free of all-cause TC and CRC, using all-cause TC, incidence of CRC, and death as a joint endpoint. 3. The above sensitivity analyses was supplemented without censoring any colectomy (regardless of type and indication) as an event.

Domaine (with reference to specific sensitivity analysis)	Description of sensitivity analysis
Competing risks for attribution of all-cause TC **Table S10**	In this sensitivity analysis the risk window was terminated if CRC (ICD-10 codes C18-C20) was diagnosed.
Missing information on the maximum extent of UC **Table S11A** **Table S11B**	For patients with lacking information: Two sets of sensitivity analysis were performed: one assuming that patients with missing information are assigned maximal disease extent (E3), and one assuming that patients with missing information are assigned minimal disease extent (E1), respectively.
Biologic therapies not included as study therapies **Table S12**	Exclusion of patients with one or more registered therapy with such therapies, *i.e.*, vedolizumab or other new biologics.
History of TP therapy in the GLM cohort **Table S13**	A comparison of outcomes was made between the TP cohort and the part of the GLM cohort that was naïve to TP therapy.
Validation of ascertainment sources for incident CRC **Table S14A (SE only)** **Table S14B**	Ascertainment of incident cases of CRC and HSTCL based on hospital discharge diagnoses was validated against registered cases of CRC and HSTCL in the national cancer registries for the part of the study period with coverage of cancer registration using the super cohort of unique patients. A sensitivity analysis was performed, examining associations between exposures and CRC as outcome, based on information available from the cancer registries in DK and SE, respectively. In DK and SE, the data coverage from the cancer registries was through 2020 and 2019, respectively. Validation was done separately for DK and SE.
Operational definitions of all-cause TC as outcome **Table S15A** **Table S15B**	1. A sensitivity analysis "to estimate the risk of "colectomy" for "intractable disease" needed to be conducted (Seq0351/1.8.2/UC Nordic (MK-8259-013) Registry Protocol 2022, Section 9.7.3). This was a request from EMA. As a proxy for identifying all-cause TC indicated by intractable disease, total colectomies performed at admissions where CRC (ICD-10: C18_C20) was registered as the primary discharge diagnosis, was excluded. All remaining total colectomies were assumed to be indicated by intractable UC. 2. The sensitivity analysis was supplemented using any colectomy (regardless of type and indication, *i.e.* all total and partial colectomies were included) as the outcome.
Risk windows without exposure to study therapies **Table S16**	To assess the effect of ignoring outcomes occurring outside risk windows, the IR of outcomes occurring outside the risk windows was estimated, using PY outside the risk windows as denominator values (that is, numerator and denominator were using the same time period to identify colectomy event and to calculate PY).
Timing of all-cause TC in relation to switching therapies **Table S17**	A 90-days period following a switch was characterized by a binary variable to indicate a new switch and the significance (indicated by the p-value) of differences across therapy cohorts was assessed.
QBA (SE only) **Table S18A** **Table S18B**	QBA (SAP, Section 9.9.4 and Annex 2) was conducted to adjust for confounding due to prior IFX exposure for all-cause TC (GLM *vs* ADA cohort)

Abbreviations used: ADA: adalimumab; CD: Crohn's Disease; CRC: colorectal cancer; DAG: directed acyclic graphs; DK: Denmark; EMA: European Medicines Agency; GLM: golimumab; HSTCL: hepatosplenic T-cell lymphoma; ICD: International Classification of Diseases; IFX: infliximab; PY: person-year; QBA: quantitative bias analysis; SE: Sweden; TC: total colectomy; TP: thiopurine; UC: ulcerative colitis

9.9.5 Amendments to the statistical analysis plan

The SAP was amended to include a coding log of the items that were observed during the programming phase and not included in the study protocol or original SAP (see SAP, Annex 5). The rationale, potential impact of the issue, and conclusion are described. Items 1-4 are related to patient demography, items 5-13 are related to data on exposures and/or outcomes, items 14-21 are related to data on covariates, and items 22-30 are related to the analysis of data. Further details are contained in Section 9.4.3.

9.10 Quality control

The study made, to a large extent, use of existing automated data, contained in central health registries established and operated for administrative purposes not related to the present study. The quality of the data in these registries is generally considered to be high, but data errors may inevitably occur[22] (see also Section 11.2.).

A range of measures were taken to control the quality of data and analyses in the various stages of the project. These measures were taken in parallel in DK as well as in SE.

Upon accessibility to central register data: Data were inspected initially concerning

- Detecting the minimum and maximum value of the quantitative variables to identify unrealistic values
- Inspecting frequency distributions of qualitative variables to detect wrong values
- Checking, as relevant, for the use of illegal codes for a given variable
- Performing logic checks of dates (such as verifying that date of death is later than date of birth and that the hospital discharge date is equal to or later than the date of hospital admission)

In programming the analyses: All analyses were overseen by two independent researchers experienced in register-based research. Programming was conducted by a primary analyst and validated by a separate analyst (validation analyst). For all data processing steps, the validation analyst reviewed the program along with input and output data sets. For the analysis steps of the project, double programming techniques were employed to reduce the potential for programming errors.

Transferring the results of analyses to report tables and figures: To reduce avoidable errors, results were exported for inclusion in report tables from the central server where the analysis was performed in a final format (*e.g.* with the agreed number of decimal values).

Blinded double checking was performed on the content of published tables for identification of potential errors.

For further details on data preparation, generation of analysis files and output report tables and figures, a reference is made to the DVP (see Stand-alone Document no. 7).

Outputting of results was automated using the Stata version of the code, except for the result for the sensitivity analysis presented in Table S3.DK that was unique for DK.

Overview of data flow

According to the study protocol, all work with data management and data analyses were carried out in separate environments in DK and SE, respectively, using the same SAP.

The plan for data preparation and analysis was developed to ensure full transparency of each step from the initial data preparation to the complete analyses.

Even though the primary data preparation and final analyses were performed using SAS software for the Danish data and Stata software for the Swedish data, cross-verification between the two software algorithms was performed and used for mutual checking to ensure comparability in the algorithms used for the data analyses.

Each step in the work was accounted for and certified in a detailed log table (see Stand-alone Document no. 8). The codes developed in DK and SE included detailed accounts of how to deal with missing data and the use of illegal codes of variables related to each of the *resource files* and *analysis files*, together with rules specifying.

Outcome of the quality control activities

The documentation of the quality control work and its results is available in Stand-alone Document no. 8 and will only briefly be summarized here, with a focus on the remaining outstanding issues.

Summary of the alignment procedure SAS versus Stata using the SE data set

The quality control process was, however, very complicated and resource demanding because of the occurrence of unexpected complex treatment trajectories in the data sets from both DK and SE. Per the protocol, the specification of establishing risk windows, assumed that patients with UC are only treated with one biologic at a time, meaning that switches between therapies should imply a short overlap period after which the new therapy should replace the previous one. In the actual final data set, commencement and continuation of alternative and competing therapies could be registered on the same date. Additionally, there were instances where two alternative therapies were administered together over extended periods of time.

Even though it was possible, with one exception, to obtain complete alignment between the results of the independently developed codes in SAS and Stata when applied to the data set from SE. The exception concerned the sensitivity analysis S1C (investigating the scenario where a 90-days lag period was applied after the date start of therapy is registered). For 15 patients (out of 3,480 patients) with complex treatment trajectories, alignment between the SAS and Stata codes could not be achieved. It was found that the Stata code reflected correctly the formation of risk windows according to the rules agreed upon. Since the Stata code was used for outputting results, this finding had no implication for the results.

Summary of the comparison of the SAS and Stata codes applied to the DK data

It was expected that running the aligned Stata code on the Danish data set would not result in discrepancies. However, this was not the case, because the Danish data contained complex data structures that did not have a match in the Swedish data and therefore could not be foreseen when aligning the code on the Swedish data. It was possible, by case-wise modification of the Stata code, to obtain complete alignment except for the formation of risk windows for 24 out

of the 5,177 patients in the analyses for all-cause TC. In all these cases the discrepancy was very small and reflected different ways for the two codes to handle unexpected treatment traction with date identity for competing treatments in various scenarios. Because the deviations were small without impacting the association analysis result and because both the Stata and the SAS codes could be justified scientifically, it was judged acceptable to apply the SAS code to the Danish data and the Stata code to the Swedish data.

9.11 Other special consideration for data management and analysis

9.11.1 Protection of Human Subjects

This study was a non-interventional observational study with no administration of any therapeutic or prophylactic agent. Patients observed in this study continued with the standard of care as provided by their physician. National registries of cancer, death, hospital contacts and socio-economic factors were the main data sources. Approval was obtained by the data agencies in the two countries prior to data extraction, management and data analysis.

9.11.2 Masking of results according to discretional rules

According to Danish and Swedish law, registry-based studies can be carried out without consent from the study subjects where the processing takes place for the sole purpose of carrying out statistical or scientific studies of significant public importance and where such processing is necessary in order to carry out these studies. It is an absolute requirement that the publication of statistical or scientific results will not reveal the identity of individuals or otherwise compromise study subjects. Following the implementation of the GDPR in EU countries including DK and SE, national regulations were issued concerning working with and publishing results of data sets obtained from national health registers. Since all data analysis in this PASS was performed in Danish settings, the Danish regulations requiring masking of results when based on small numbers were followed. The regulations relevant to this PASS are summarized below:

- *Overall:* Any aggregate count of persons or events that are explicitly based on or may be back-calculated to number of persons, must be masked if the aggregate number is >0 and <5.
- *2x2 contingency tables:* All cell values in the content must be masked for values >0 and <5 in one or more of the cells.
- *2xn contingency tables:* Both content cells in the row must be masked if at least one of the cell values is >0 and <5. Furthermore, the content of one cell in another row (selected by the user) of the column with an impermissible value must be masked.
- *kxn contingency tables:* If a cell contains an impermissible value, the cell content must be masked together with masking one additional cell in the same row and one additional cell in the same column (both selections made on user's discretion).
- *Non-parametric measures (including min, max, median, quartiles):*

- Min and max values must be masked
- A median value must be masked unless based on a sample >5 persons
- Quartile values must be masked unless based on >5 persons

- *Point estimates (including IRs and IRRs, with 95% CIs):* If based on <5 persons, point estimates and their 95% CIs must be masked.
- *Graphical presentations depicting individual observations, such as Kaplan-Meier plots:* Such graphics are not permissible (N.P.).

In the presentation of results 'N.P.' was used for masked results. This must be distinguished from 'N.A.' (not applicable) which was used when the content was irrelevant.

Another limitation implied by the GPDR is that no data or information referring to individual subjects (so-called micro data) must be exported from the secure analysis environment. The same applies to aggregated data containing counts of events >0 and <5.

The meta-analysis was based on aggregated data from DK and SE on outcomes and person-time of exposure. For this analysis, aggregated data was exported from separate analysis environments and brought into a common analysis environment. The software offered no option for the inclusion of covariates.

10 RESULTS

10.1 Participants

In total, 12,646 unique patients (DK: 5,177; SE: 7,469) were enrolled. Figures D1.DK and D1.SE illustrate the identification of the study populations in each country, from the total registered population of patients with UC after applying exclusion criteria.

Text Table 6A summarizes the population of unique patients by initial study entry.

Text Table 6A. Overview of patients by initial therapy cohort.

	GLM cohort n	Other Anti-TNF cohort n	TP cohort n	Total n
DK	199 (4%)	2,630 (51%)	2,348 (45%)	5,177 (100%)
SE	151 (2%)	2,172 (29%)	5,146 (69%)	7,469 (100%)
Total	350 (3%)	4,802 (38%)	7,494 (59%)	12,646 (100%)

Abbreviations used: DK: Denmark; GLM: golimumab; SE: Sweden; TNF: tumor necrosis factor; TP: thiopurine

The proportion of patients having GLM as their initial therapy cohort was 3% (4% in DK, 2% in SE) and 38% of the patients had Other Anti-TNF as their initial therapy cohort. In DK, the latter proportion was substantially higher than in SE (51% versus 29%). Conversely, only 45% of the DK patients had TP as their initial therapy cohort compared to 69% of the SE patients (overall 59% patients had TP as their initial therapy). DK patients comprised 41% of the total population of unique patients. See also Table D3.DK and Table D3.SE.

The distribution of the patients (including patients at initial study entry and patients who switched therapy during follow-up) is presented in Text Table 6B, see also Figures D2.DK and D2.SE. Thus, an individual patient is counted in each of the therapy cohorts to which the patient is contributing person-time. The total amount of PY by country and therapy cohort is also shown.

Text Table 6B. Overview of patients by therapy cohort.

	GLM cohort n (PY)	**Other Anti-TNF cohort n (PY)**	**TP cohort n (PY)**	**Total[a] n (PY)**
DK	595 (2,001.4)	3,676 (13,385.3)	2,348 (10,288.4)	6,619 (25,675.1)
SE	298 (1,285.7)	3,385 (11,247.4)	5,146 (19,803.5)	8,829 (32,336.6)
Total	893 (3,287.1)	7,061 (24,632.7)	7,494 (30,091.9)	15,448 (58,011.7)

Abbreviations used: DK: Denmark; GLM: golimumab; PY: person-years; SE: Sweden; TNF: tumor necrosis factor; TP: thiopurine

[a] A given patient may contribute to more than one cohort after therapy switch

When comparing the relative distribution of patients by therapy cohort in Text Table 6B (allowing patient to contribute to more than one cohort based on therapy switches) to Text Table 6A (initial therapy cohort), the number of patients in the GLM cohort increased in both

DK and SE. This suggests that GLM therapy was used after treatment with other study therapies.

In terms of demographic and clinical characteristics, the DK and SE populations had similar profiles with a few exceptions. The relative number of patients in the TP cohort was lower in DK (45%) than in SE (69%). A prior history of having experienced a lower endoscopy within one year before cohort entry was higher in DK (82%) than in SE (70%). A prior history of therapy with TP in the GLM and Other Anti-TNF combined was lower in DK (37%) than in SE (55%) (see Tables D2A.DK and D2A.SE).

In the super cohort, the number of deaths registered after enrolment and before end of follow-up was 318 (DK:161, SE: 157). The number of patients registered as emigrants was 44 (DK: 25, SE: 19). No other dropouts were registered (data not shown in tables).

10.2 Descriptive data

Tables D1.DK and D1.SE expand Figures D2.DK and D2.SE by showing the accrual of new entries to therapy cohorts and corresponding person-time of exposure by calendar year. Patients were counted in each cohort entered at least once. In the *unique* population of patients, 62% (63% in DK, 62% in SE) of the patients were enrolled in the study before 2018.

Tables D2A.DK and D2A.SE present the clinical characteristics of the unique patient populations in DK and SE, respectively, by the initial therapy cohort at study entry.

The patient populations in DK and SE had many similar features. Overall, 47% (44% in DK, 50% in SE) of the patients aged <35 years; 53% (50% in DK, 55% in SE) were males; 62% (63% in DK, 62% in SE) had a duration of UC <5 years at entry to the initial therapy cohort; 22% (21% in DK, 23% in SE) had at some time in their disease history, a diagnosis of CD registered; 75% (82% in DK, 70% in SE) had at least one lower endoscopy in the year prior to entry to the initial therapy cohort. The number of patients with a history of therapy with cyclosporine (proxy for more advanced therapy) and a history of other comorbidities were too small to allow comparisons.

From the data in Tables D2A.DK and D2A.SE, it can be calculated that for the sub-population of patients in the initial therapy cohorts GLM and Other Anti-TNF combined, 13% (15% in DK and 9% in SE) had a history of therapy with at least one biologic therapy at entry to the initial therapy cohort. In the same sub-population 45% (37% in DK and 55% in SE) had a positive history of therapy with TP at entry to the initial therapy cohort.

Tables D2B.DK and D2B.SE show the clinical characteristics of the patient populations in DK and SE, respectively, at the first entry to a therapy cohort including patients entered initially at study entry and entered after therapy switch during follow-up. Thus, if patients switched to another therapy during the observation period they were included in the new therapy cohort as well and contributing more than once in the table. There were both similarities and differences across cohorts and between countries. In DK (Tables D2B.DK), the proportion of patients with a long duration of UC (≥10 years) was higher in the GLM cohort than in the other cohorts (30.9% versus 22.9% and 17.0% for the Other Anti-TNF and the TP cohort, respectively). Compared with the Other Anti-TNF cohort, more patients in the GLM cohort had a positive

history of prior TP therapy (78.7% versus 52.6%) and fewer patients were naïve to biologics at first cohort entry (10.8% versus 91.2%). In SE (Table D2B.SE), the proportion of patients with a long duration of UC (≥10 years) was also higher in the GLM cohort than in the other cohorts (40.3% versus 29.0% and 17.0% for the Other Anti-TNF and the TP cohort, respectively). Compared with the Other Anti-TNF cohort, fewer patients in GLM cohort were naïve to biologics at cohort entry (39.9% versus 94.5%). The proportion of patients with early entry to the GLM cohort was higher in SE than in DK (72.1% of the patients in the GLM cohort in SE had entry before 2018 against 54.1% in the corresponding patients in DK). For particularly the GLM cohort, relatively more patients were naïve to biologic therapy prior to therapy cohort entry in SE (39.9%) than in DK (10.8%).

Tables D3.DK and D3.SE show the pattern of switches to the second therapy cohort. As per definition, patients entering the GLM or the Other Anti-TNF cohort could not subsequently enter the TP cohort. In both DK and SE, <20% of patients in the GLM and Other Anti-TNF initial cohorts switched to an alternative study therapy (Other Anti-TNF or GLM). For patients with TP as the initial cohort, there was a marked difference between DK and SE as far as the subsequent switch to either GLM or the Other Anti-TNF cohort. Specifically, in DK, 56% of the patients stayed in the TP cohort while <1% had GLM and 43% had Other Anti-TNF as the second therapy cohort, whereas in SE 76% of the patients stayed in the TP cohort while <1% had GLM and 23% had Other Anti-TNF as the second therapy cohort. The unique study patients were characterized at the initial cohort entry according to status on subsequent switches by selected covariates and stratified by initial therapy cohort in Tables D4.DK and D4.SE. The patterns were similar in DK and SE without any major differences in the distributions by covariates with each initial therapy cohort.

Tables D5.DK and D5.SE show the distribution of patients by selected covariates at the occurrence of outcomes, stratified by therapy cohort. Note that patients entering more than one therapy cohort are included multiple times in the absolute number of outcomes observed. For the CRC outcome, only limited data may be shown due to masking rules. Overall, there were no major differences between therapy cohorts and between DK and SE.

The initial selection and parametrization of covariates shown in Text Table 2, were based on expectations. Due to the structure of the real-life data, the need to optimize the categorization of covariates in the adjusted statistical analyses and the need to avoid as much as possible the masking of information, it was necessary to change the parametrization for several covariates. Text Table 7 accounts for the final list and categorization of covariates, as used in the primary association analyses. A detailed account of amendments made can be found in the SAP, Annex 5.

Text Table 7. Final parametrization of covariates and their inclusion in the adjusted analyses. See Section 9.4.3 in this report and SAP, Annex 1 for codes defining diseases and conditions.

Covariate	Final parametrization	CRC as the outcome		Al-cause TC as the outcome	
		DAG adjustment[a]	Full adjustment[b]	DAG adjustment[a]	Full adjustment[b]
Country	1: DK (Denmark) 2: SE (Sweden)	[c]	[c]	[c]	[c]
Sex	1: Males 2: Females	No	Yes[d]	No	Yes
Age	1: <34 years 2: ≥35 years	Yes[d]	Yes[d]	Yes	Yes
Disease duration	0: 0-4 years 5: 5-9 years 10: ≥10 years	Yes[d]	Yes[d]	Yes	Yes
Calendar year	1: <=2017 2: >2017	Yes[d]	Yes[d]	Yes	Yes
Extent of UC	1: E1 (Ulcerative proctitis) 2: E2 (Left sided (distal) UC 3: E3 Extensive UC (pancolitis) 9: Unclassifiable extent	Yes[d]	Yes[d]	Yes	Yes
Colonoscopies, flexible sigmoidoscopies	0: No procedure registered 1: One procedure registered 2: ≥2 procedures registered	No	Yes[d]	No	Yes
History of treatment with steroids	0: <2 episodes of steroid treatment registered 1: ≥2 episodes of steroid treatment registered	No	Yes[d]	Yes	Yes
History of treatment with cyclosporin	0: No 1: Yes	No	No	No	No
Prior history of sclerosing cholangitis[e]	0: No	Yes[d]	Yes[d]	Yes	Yes

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	1: Yes				
Prior history of arthropathies[e]	0: No 1: Yes	No	Yes[d]	No	Yes
Prior history of psoriasis[e]	0: No 1: Yes	No	Yes[d]	No	Yes
Prior history of Crohn's Disease[e]	0: No 1: Yes	No	Yes[d]	No	Yes
History of treatment with TP	1: >1 episode of treatment with TP registered 0: No episode of treatment with TP registered	No	Yes[d, f]	No	Yes[f]
History of treatment with biologics	1: No prior therapy with a biologic 2: At least one prior therapy with a biologics	No	Yes[d, f]	Yes	Yes[f]

Abbreviations used: CRC: colorectal cancer; DAG: directed acyclic graphs; GLM: golimumab; TC: total colectomy; TP: thiopurine; UC: ulcerative colitis

[a] Included in the minimal adjustment set from the DAG process (see SAP, Annex 4) unless otherwise specified in the analysis

[b] Included in the fully adjusted analyses unless otherwise specified in the analysis

[c] Only included in the analysis combining data from DK and SE

[d] Due to small numbers, results will be masked and cannot be presented

[e] Captured from primary or secondary discharge diagnoses

[f] Not included as a covariate for the comparison between GLM and TP

10.3 Outcome data

Text Table 8A reviews the study persons and outcomes in DK and SE.

Text Table 8A. Overview of unique patients in the super cohort and outcomes in DK and SE.

	DK	SE
Study patients		
Total numbers	5,177	7,469
Patients <35 at entry to initial therapy cohort (%)	2,261 (43.7)	3,726 (49.9)
Males (%)	2,611 (50.4)	4,120 (55.2)
Duration of UC < 5 years at entry to initial therapy cohort (%)	3,254 (62.9)	4,602 (61.6)
Colorectal cancer		
Number of cases	27	41
Total PY	23,137.4	28,261.2
Crude IR per 1,000 PY[a]	1.2	1.5
95% CI	0.8, 1.7	1.0, 2.0
All-cause TC		
Number of cases	686	474
Total PY	20,751.6	26,863.3
Crude IR per 1,000 PY[a]	33.1	17.6
95% CI	30.6, 35.6	16.1, 19.3

Abbreviations used: DK: Denmark; CI: confidence interval; IR: incidence rate; PY: person-years; SE: Sweden; TC: total colectomy; UC: ulcerative colitis;
[a] The IR is based on all outcomes registered and total person-time from cohort entry through end of observation, regardless of exposure to study therapies

The total number of study patients enrolled in DK and SE was 5,177 and 7,469, respectively. Approximately 50% of the study persons were males in both countries and slightly less than 50% of the patients were <35 years at entry to the initial therapy cohort. Slightly more than 60% of the patients had <5 years of duration since the first registered diagnosis of UC at entry to the first treatment cohort (Text Table 8A).

During the study enrolment and follow-up period, 68 cases of CRC (DK: 27; SE: 41) and 1,160 cases of all-cause TC (DK: 686; SE: 474) were registered (Text Table 8A, Figures D3.DK and D4.DK). Using all outcomes and person-time observed regardless of exposure to study therapies, it may be possible to estimate IRs that are assumed to be representative of the population of patients with moderate to severe UC. For CRC, the IRs were similar in DK and SE (1.2 (95% CI: 0.8, 1.7) per 1,000 PY versus 1.5 (95% CI: 1.0, 2.0)). In contrast, the IR of all-cause TC was almost twice as high in DK as in SE (33.1 (95% CI: 30.6, 35.6) per 1,000 PY versus 17.6 (95% CI: 16.1, 19.3)).

No cases of HSTCL were ascertained.

Figures D3.DK and D3.SE were intended to show Kaplan-Meier plots of the cumulative incidence of CRC in the population of unique patients regardless of therapy cohorts; however,

due to the masking rules, summary data are tabulated together with the crude IR of CRC. See also Text Table 8A.

Figures D4.DK and D.4SE were intended to show Kaplan-Meier plots of the cumulative incidence of all-cause TC in the population of unique patients regardless of therapy cohorts; however, due to the masking rules, the summary data are tabulated together with the crude IR of all-cause TC. See also Text Table 8A.

Tables D6A.DK and D6A.SE expand the information in Text Table 8A by showing the number of outcomes and corresponding IRs by therapy cohorts. Patients who entered more than one therapy cohort are counted for each cohort and thereby contributing more than once. In this analysis, all outcomes and all person-time from first therapy cohort entry until end of observation were included. For the crude IR of all-cause TC, the same gradient in DK and SE was seen, with the highest IR in the GLM cohort, followed by the IR in the Other Anti-TNF cohort, and with the lowest rate in the TP therapy category. The colectomy rate was substantially higher in DK for all therapy cohorts compared to SE, but the difference was less for the TP cohort (IR in DK: 18.5 (95% CI: 16.0, 21.3) versus 13.8 (95% CI: 12.2, 15.6) in SE. The IRs for the Other Anti-TNF cohort was 44.2 (95% CI: 40.8, 47.9) in DK and 28.9 (95% CI: 25.8, 32.4) in SE and those for the GLM cohort 57.5 (95% CI: 47.9, 69.0) in DK and 35.9 (95% CI: 26.4, 48.8) in SE. Due to the masking rules, only limited results are available for CRC as the outcome. In DK, the IR of CRC was 1.0 (95% CI: 0.6, 1.7) for the Other Anti-TNF cohort, and in SE the IR of CRC was 1.1 (95% CI: 0.7, 1.7) for the TP cohort.

Tables D6B-D.DK and D6B-D.SE show the same data with stratification for history of therapy with prior biologics (0 biologics: Tables D6B.DK and D6B.SE; 1 biologic: Tables D6C.DK and D6C.SE; 2 or more biologics: Tables D6D.DK and D6D.SE) at the first time entering a therapy cohort. For all-cause TC as the outcome and with no prior history of therapy with biologics, the colectomy rate in the GLM cohort was 23.2 per 1,000 PY (95% CI: 11.1, 48.7) as compared to 45.9 (95% CI: 42.2, 49.9) in the Other Anti-TNF, and 18.5 per 1,000 PY (95% CI: 16.0, 21.3) in the TP therapy cohort in DK. Similarly in this stratum in SE, the colectomy rate in GLM was 29.7 per 1,000 PY (95% CI: 18.2, 48.4) as compared to 28.9 (95% CI: 25.7, 32.5) in the Other Anti-TNF, and 13.8 (95% CI: 12.2, 15.6) in TP therapy cohort. For the stratum with 1 prior biologic in DK, the colectomy rate in the GLM cohort was 62.6 per 1,000 PY (95% CI: 50.1, 78.2); the number can not be shown in the Other Anti-TNF cohort due to masking. For the same strata in SE, the colectomy rate in the GLM cohort was 39.2 per 1,000 PY (95% CI: 25.0, 61.4) and 29.6 (95% CI: 19.1, 45.9) in the Other Anti-TNF cohort. For the stratum with 2 or more biologics, data were too scarce to provide any valid inference. For CRC as the outcome, stratified data were too scarce to provide any valid inference.

10.4 Main results

No cases of HSTCL were observed and this outcome is not further explored in this final report.

This section presents the primary association analyses for CRC and all-cause total colectomies as outcomes separately. Within each analysis, comparisons are made between GLM and Other Anti-TNF therapies and between GLM and TP therapies.

During the preparation of the SAP, it was decided, for all-cause TC, to include a separate category representing overlapping risk windows between GLM and Other Anti-TNF, as some patients were exposed to both therapies at the same time. However, it became necessary to collapse categories in order to avoid further masking of results due to small numbers in the overlap category. Since the GLM therapy category in the comparison between GLM and TP contained the overlap category of both GLM and Other Anti-TNF, it was decided to combine the risk time with GLM and risk time with overlapping exposure of both GLM and Other Anti-TNF.

The protocol specified use of Cox proportional hazard regression model techniques in the association analysis, with Poisson regression analysis as the alternative. Log-log plots of the hazard rates revealed, for both the DK and the SE patient population, that the proportional hazards assumption of using Cox proportional hazards regression analyses was not fulfilled. Due to masking rules, it is not permitted to show these plots. Accordingly, the Poisson regression analysis was used for the primary association analyses and the sensitivity analyses. For a sample of the analyses, Cox regression analysis was also applied (not shown for the reasons cited above), which generated results very similar to the Poisson regression analysis.

Tables P1A, P1B, P2A and P2B present the results of the Poisson regression analysis. These tables present the crude IRRs in the top row and the adjusted IRRs in the DAG model and in the final full adjusted model in the bottom rows (see Text Table 7 for covariates included in the models). Information on each covariate is also shown with numbers of outcomes and PY at risk for each stratum of the covariate across therapy categories, and with IRRs representing the inclusion of each covariate separately together with exposure categories in the analysis.

Text Table 8B summarizes the results of the primary association analyses for CRC as the outcome. However, due to the masking rules, the results of the analyses for CRC as the outcome cannot be shown. The detailed results including information on covariates are presented in Tables P1A.DK, P1B. DK, P1A.SE, and P1B.SE.

Text Table 8C summarizes the results of the primary association analyses for all-cause TC as the outcome. The detailed results including information on covariates are presented in Tables P2A.DK, P2B.DK, P2A.SE, and P2B.SE.

The results are commented below.

Text Table 8B. CRC as the outcome. Overview of results of main association analyses.

Comparison: GLM versus Other Anti-TNF	N	PY	Crude IR per 1000 PY (95% CI)	IRR_crude (95% CI)	IRR_DAG[a] (95% CI)	IRR_Final[b] (95% CI)
DK						
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	**N.P.**	**N.P.**	**N.P.**
Other Anti-TNF	N.P.	N.P.	N.P.	**1.0 (ref.)**	**1.0 (ref.)**	**1.0 (ref.)**
SE						
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	**N.P.**	**N.P.**	**N.P.**
Other Anti-TNF	N.P.	N.P.	N.P.	**1.0 (ref.)**	**1.0 (ref.)**	**1.0 (ref.)**
Comparison: GLM versus TP	**N**	**PY**	**per 1000 PY (95% CI)**	**IRR_crude (95% CI)**	**IRR_DAG[c] (95% CI)**	**IRR_Final[d] (95% CI)**
DK						
GLM (incl. overlap with other Anti-TNF)	<5	N.P.	N.P.	**N.P.**	**N.P.**	**N.P.**
TP	N.P.	N.P.	N.P.	**1.0 (ref.)**	**1.0 (ref.)**	**1.0 (ref.)**
SE						
GLM (incl. overlap with other Anti-TNF)	<5	N.P.	N.P.	**N.P.**	**N.P.**	**N.P.**
TP	N.P.	N.P.	N.P.	**1.0 (ref.)**	**1.0 (ref.)**	**1.0 (ref.)**

Abbreviations used: CI: confidence interval; CRC: colorectal cancer; DK: Denmark; GLM: golimumab; IR: incidence rate; IRR: incidence rate ratio; PY: person-years; N.P.: not permissible; SE: Sweden; TNF: tumor necrosis factor; TP: thiopurine

[a] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, history of sclerosing cholangitis

[b] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, history of CD, history of therapy with TP, and history of therapy with biologics

[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, histories of sclerosing cholangitis

[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, and history of CD

Text Table 8C. All-cause TC as the outcome. Overview of results of main association analyses.

Comparison: GLM versus Other Anti-TNF	N	PY	Crude IR per 1000 PY (95% CI)	IRR_crude (95% CI)	IRR_DAG[a] (95% CI)	IRR_Final[b] (95% CI)
DK						
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)	**1.5 (1.2, 1.9)**	**1.3 (1.0, 1.7)**	**1.3 (1.0, 1.6)**
Other Anti-TNF	410	7,647.2	53.6 (48.7, 59.1)	**1.0 (ref.)**	**1.0 (ref.)**	**1.0 (ref.)**
SE						
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	**1.4 (0.9, 2.3)**	**1.2 (0.7, 1.9)**	**1.1 (0.7, 1.8)**
Other Anti-TNF	162	6,094.3	26.6 (22.8, 31.0)	**1.0 (ref.)**	**1.0 (ref.)**	**1.0 (ref.)**
Comparison: GLM versus TP	**N**	**PY**	**per 1000 PY (95% CI)**	**IRR_crude (95% CI)**	**IRR_DAG[c] (95% CI)**	**IRR_Final[d] (95% CI)**
DK						
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)	**10.4 (6.7, 16.0)**	**13.6 (8.7, 21.3)**	**12.7 (8.1, 19.8)**
TP	27	3,540.9	7.6 (5.2, 11.1)	**1.0 (ref.)**	**1.0 (ref.)**	**1.0 (ref.)**
SE						
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	**4.4 (2.7, 7.0)**	**4.5 (2.7, 7.4)**	**3.9 (2.3, 6.4)**
TP	92	10,455.1	8.8 (7.2, 10.8)	**1.0 (ref.)**	**1.0 (ref.)**	**1.0 (ref.)**

Abbreviations used: CI: confidence interval; CRC: colorectal cancer; DK: Denmark; GLM: golimumab; IR: incidence rate; IRR: incidence rate ratio; PY: person-years; N.P.: not permissible; SE: Sweden; TC: total colectomy; TNF: tumor necrosis factor; TP: thiopurine

[a] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, history of sclerosing cholangitis, history of therapy with steroids, and history of therapy with biologics

[b] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, history of CD, history of therapy with TP, and history of therapy with biologics. History of arthropathies was excluded due to lack of data in the Danish data set

[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, history of therapy with steroids, history of sclerosing cholangitis

[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of psoriasis, and history of CD. History of arthropathies was excluded due to lack of data in the Danish data set

10.4.1 Association analyses with CRC as the outcome

The detailed results are presented in Tables P1A.DK and P1A.SE for the comparison between GLM and Other Anti-TNF, and in Tables P1B.DK and P1B.SE for the comparison between GLM and TP.

Due to the masking rules, it was not possible to show either the crude or adjusted IRR-values. Even considering wide 95% CIs, the IRR-values were close to unity in both DK and SE and for both comparisons between GLM and Other Anti-TNF and between GLM and TP. Thus, even despite the need to mask the results, there was no evidence of increased risk of CRC for therapy with GLM compared with Other Anti-TNF and with TP.

As supplementary information, IRs of CRC were calculated for each level of every covariate with grouping of outcomes and risk time over exposure categories. For the few covariates where results could be shown for the comparison between GLM and Other Anti-TNF (Tables P1A.DK and P1A.SE), the IRs of CRC were at the same magnitude as shown in Figures D3.DK and D3.SE, respectively. For example, in DK the IRs <2018 and ≥2018 were 1.2 per 1,000 PY (95% CI: 0.5, 3.0) and 0.8 (95% CI: 0.4, 1.6), respectively. The IR was 1.9 (95% CI: 1.0, 3.7) for duration of UC ≥10 years. The IR of CRC without a positive history of prior biologic therapy was 1.0 (95% CI: 0.6, 1.7). In SE, the IR of CRC without a positive history of prior biologic therapy was 1.8 (95% CI: 1.2, 2.9). For the remaining available results, the IRs were of similar magnitude within each country. The IRs of CRC were in general slightly higher in SE than in DK but 95% CIs were overlapping.

For the few covariates where results could be shown for the comparison between GLM and TP (Tables P1B.DK and P1B.SE), the IRs of CRC were at the same magnitude as shown in Figures D3.DK and D3.SE, respectively. For the remaining available results, the IRs were at similar magnitude within each country. There was not sufficient information to compare the level of IRs between DK and SE.

10.4.2 Association analyses with all-cause TC as the outcome

Overall, the IR of all-cause TC was substantially higher in DK than in SE for GLM and Other Anti-TNF. In DK, the IRs for GLM (including overlap period) and Other Anti-TNF were 79.0 per 1,000 PY (95% CI: 63.8, 97.7) and 53.6 (95% CI: 48.7, 59.1), respectively (Table P2A.DK). The corresponding point estimates for SE were 38.5 (95% CI: 25.1, 59.0) and 26.6 (95% CI: 22.8, 31.0), respectively (Table P2A.SE). In contrast, the IR of all-cause TC was of similar magnitude in the two countries for the TP cohort. In DK, the IR for TP was 7.6 (95% CI: 5.2, 11.1) (Table P2B.DK). The corresponding point estimate for SE was 8.8 (95% CI: 7.2, 10.8) (Table P2B.SE).

The all-cause TC detailed results are presented in Tables P2A.DK and P2A.SE for the comparison between GLM and Other Anti-TNF. The crude IRR was similar in DK and SE (for DK: 1.5 (95% CI: 1.2, 1.9) and for SE: 1.4 (95% CI: 0.9, 2.3)). In DK, the adjusted IRRs in the DAG model and the fully adjusted model were reduced to 1.3 (95% CI: 1.0, 1.7), and 1.3 (95% CI: 1.0, 1.6), respectively. In SE, the adjusted IRRs were reduced to 1.2 (95% CI: 0.7, 1.9) for the DAG adjusted and 1.1 (95% CI: 0.7, 1.8) for the fully adjusted IRR, and neither

the crude nor the adjusted IRR-values showed statistical significance as assessed by the 95% CIs.

For the covariates where results could be shown (Tables P2A.DK and Table P2A.SE), the IRs of all-cause TC varied between levels of covariates and between DK and SE. Overall, the IRs in DK were about twice those in SE. In DK, the IRs <2018 and ≥2018 were 96.9 per 1,000 PY (95% CI: 86.5, 108.5) and 34.9 (95% CI: 30.3, 40.1), respectively. The IR was 87.7 (95% CI: 78.9, 97.5) for duration of UC <5 years but only 29.9 (95% CI: 23.5, 38.1) and 33.2 (95% CI: 26.9, 40.9) for durations at 5-9 years and ≥10 years, respectively. The IR was 84.6 (95% CI: 73.9, 96.9) for a positive history of recent therapy with systemic steroid and 45.7 (95% CI: 40.7, 51.4) with a negative history. The IR was 91.3 (95% CI: 78.6, 105.9) for a history of ≥2 recent lower endoscopies but only 50.9 (95% CI: 42.8, 60.5) and 45.0 (95% CI: 39.0, 51.8) for 1 and 0 recent endoscopies, respectively. The IR was 102.1 (95% CI: 88.9, 117.3) with a negative history of prior TP therapy but only 43.7 (95% CI: 39.0, 49.0) with a positive history. In SE, the IRs <2018 and ≥2018 were 42.8 (95% CI: 35.5, 51.6) and 17.8 (95% CI: 14.1, 22.4), respectively. The IR was 45.4 (95% CI: 37.6, 54.8) for duration of UC <5 years but only 20.5 (95% CI: 14.8, 28.3) and 15.2 (95% CI: 11.0, 21.0) for durations at 5-9 years and ≥10 years, respectively. The IR was 49.8 (95% CI: 41.3, 60.0) for a positive history of recent therapy with systemic steroid and 16.5 (95% CI: 13.1, 20.7) with a negative history. The IR was 64.1 (95% CI: 51.4, 80.0) for a history of ≥2 recent lower endoscopies but only 25.0 (95% CI: 18.8, 33.3) and 16.4 (95% CI: 12.7, 21.2) for 1 and 0 recent endoscopies, respectively. In contrast with the findings in DK, there was no difference with respect to a positive versus a negative history of TP therapy.

The detailed results are presented in Tables P2B.DK and P2B.SE for the comparison between GLM and TP. The crude IRR for all-cause TC was increased in both countries: for DK 10.4 (95% CI: 6.7, 16.0) and for SE 4.4 (95% CI: 2.7, 7.0). In DK, the IRR-value increased from 10.4 to 13.6 in the DAG adjusted model and to 12.7 in the fully adjusted model. The 95% CIs were large but above the null value. In SE, the IRR-value was changed from 4.4 to 4.5 in the DAG adjusted model and was reduced from 4.4 to 3.9 in the fully adjusted model; the 95% CIs were large but above the null value. In this analysis, the covariates related to prior history of therapy with biologics and a prior history of therapy with TP, were excluded because patients contributing to the TP category had to be naïve to both TP and biologics at cohort entry.

For the covariates where results could be shown (Tables P2B.DK and P2B.SE), the IRs of all-cause TC varied between levels of covariates and between DK and SE. Overall, the IRs in DK were about twice those in SE.

In DK, the IRs for <2018 and ≥2018 were 38.4 per 1,000 PY (95% CI: 30.5, 48.4) and 14.6 (95% CI: 10.7, 19.9), respectively. The IR was 40.3 (95% CI: 31.0, 52.5) for a positive history of recent therapy with systemic steroid and 17.5 (95% CI: 13.5, 22.7) with a negative history. In SE, the IRs for <2018 and ≥2018 were 14.2 (95% CI: 11.2, 18.1) and 7.4 (95% CI: 5.6, 9.8), respectively. The IR was 15.9 (95% CI: 12.4, 20.5) for a positive history of recent therapy with systemic steroid and 7.3 (95% CI: 5.6, 9.6) with a negative history. The IR was 29.5 (95% CI: 22.6, 38.6) for a history of ≥2 recent lower endoscopies but only 7.2 (95% CI: 4.8, 11.0) and 6.2 (95% CI: 4.5, 8.5) for 1 and 0 recent endoscopies, respectively.

10.4.3 Meta-analysis: Analysis of aggregated data from DK and SE

A combined estimate for DK and SE of the association between therapy and CRC, and between therapy and all-cause TC was obtained in a meta-analysis using aggregated data from DK and SE applying the M-H method for person-time data. The software used for the meta-analysis did not offer the possibility to adjust for covariates.

Text Table 9A shows the results from DK and SE for CRC as the outcome. As in the case for the country-specific analyses (Tables P1A.DK, P1B.DK and P1A.SE, P1B.SE, respectively), the masking rules prohibited presenting the results of the analysis.

Text Table 9B shows the results from DK and SE for all-cause TC as the outcome. The unadjusted M-H estimate of the IRR for the association between GLM and Other Anti-TNF was 1.5 (95% CI: 1.2, 1.8) and close to the crude IRR-values within SE and DK (Table P2A.DK and P2A.SE, respectively and Text Table 8C, upper panel). This was also reflected with a I^2-value of 0% and no statistical evidence of heterogeneity (P=0.95 in the Q-test). The consistency in the association estimates for DK and SE was evident even in spite of the fact that the IR for all-cause TC was twice as high in DK than in SE for both GLM and Other Anti-TNF.

The unadjusted M-H estimate of the IRR for the association between GLM and TP was 7.8 (95% CI: 5.7, 10.9) which was in the middle of the range between the fully adjusted IRR at 12.7 in DK (Table P2B.DK and Text Table 8C, lower panel) and the corresponding value at 3.9 in SE (Table P2B.SE and Text Table 8C, lower panel). This dispersion was supported by a I^2-value as high as 86% and a strong statistical evidence of heterogeneity (P=0.007 in the Q-test). Whereas the IR of all-cause TC was twice as high in DK than in SE for GLM, the IRs were at the same low level for TP in the two countries.

It should be noted that the I^2-value may be subject to bias when only few studies are included.[34]

Text Table 9A. Meta-analysis combining results from DK and SE. CRC as the outcome.

Upper panel: GLM (incl. overlap with Other Anti-TNF) versus Other Anti-TNF; lower panel: GLM (incl. overlap with Other Anti-TNF) versus TP.

GLM (incl. overlap) versus Other Anti-TNF	Number N	Person-years PY[a]	Crude IR per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. overlap) (95% CI)	Other Anti-TNF (ref)
Data (see Table P1A)				**N.P.**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF): DK	<5	N.P.	N.P.		
GLM (incl. overlap with Other Anti-TNF): SE	<5	N.P.	N.P.		
Other Anti-TNF: DK	N.P.	N.P.	N.P.		
Other Anti-TNF: SE	N.P.	N.P.	N.P.		
				Summary statistics: **Mantel-Haenszel (effect):** **N.P** **I^2 (heterogeneity):** **N.P** **Q-test (heterogeneity):** **N.P**	

GLM versus TP	Number N	Person-years PY[a]	Crude IR per 1000 PY (95% CI)	IRR[b]	
				GLM) (95% CI)	TP (ref)
Data (see Table P1B)				**N.P.**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF): DK	<5	N.P.	N.P.		
GLM (incl. overlap with Other Anti-TNF): SE	<5	N.P.	N.P.		
TP: DK	N.P.	N.P.	N.P.		
TP: SE	N.P.	N.P.	N.P.		
				Summary statistics: **Mantel-Haenszel (effect):** **N.P** **I^2 (heterogeneity):** **N.P** **Q-test (heterogeneity):** **N.P**	

Abbreviations: CI: confidence interval; GLM: golimumab; IR: incidence rate; N.P.: not permissible; PY: person-years; TNF: tumor necrosis factor alpha; TP: thiopurine.

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4.

[b] IRR: Incidence rate ratio obtained as weighted Mantel-Haenszel estimate, unadjusted for covariates.

Text Table 9B. Meta-analysis combining results from DK and SE. All-cause TC as the outcome.

Upper panel: GLM (incl. overlap with Other Anti-TNF) versus Other Anti-TNF; lower panel: GLM (incl. overlap with Other Anti-TNF) versus TP.

GLM (incl. overlap) versus Other Anti-TNF	Number N	Person-years PY[a]	Crude IR per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. overlap) (95% CI)	Other Anti-TNF (ref)
Data (see Table P2A)				**1.5 (1.2, 1.8)**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF): DK	85	1,076.5	79.0 (63.8, 97.7)		
GLM (incl. overlap with Other Anti-TNF): SE	21	545.7	38.5 (25.1, 59.0)		
Other Anti-TNF: DK	410	7,646.2	53.6 (48.7, 59.1)		
Other Anti-TNF: SE	162	6,094.3	26.6 (22.8, 31.0)		
				Summary statistics:	
				Mantel-Haenszel (effect):	**P<0.001**
				I^2 (heterogeneity):	**0.0%**
				Q-test (heterogeneity):	**P=0.95**

GLM versus TP	Number N	Person-years PY[a]	Crude IR per 1000 PY (95% CI)	IRR[b]	
				GLM) (95% CI)	TP (ref)
Data (see Table P2B)				**7.8 (5.7, 10.9)**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF): DK	85	1,076.5	79.0 (63.8, 97.7)		
GLM (incl. overlap with Other Anti-TNF): SE	21	545.7	38.5 (25.1, 59.0)		
TP: DK	27	3,540.9	7.6 (5.2, 11.1)		
TP: SE	92	10,455.1	8.8 (7.2, 10.8)		
				Summary statistics:	
				Mantel-Haenszel (effect):	**P<0.0001**
				I^2 (heterogeneity):	**86.1%**
				Q-test (heterogeneity):	**P=0.007**

Abbreviations: CI: confidence interval; GLM: golimumab; IR: incidence rate; PY: person-years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine.

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4.

[b] IRR: Incidence rate ratio obtained as weighted Mantel-Haenszel estimate, unadjusted for covariates.

10.5 Sensitivity analyses

A series of sensitivity analyses was established to assess the extent to which the results of the primary association analyses were affected by alternative definitions of risk windows, ascertainment of outcomes, and certain covariates. Results for CRC as the outcome were not presented due to masking rules for small numbers and the number of outcomes was further reduced in most of the sensitivity analyses making any inference meaningless. For the results concerning all-cause TC as the outcome, point estimates (with IR per 1,000 PYs) are presented with 95% CIs in parenthesis. Text Table 5 contains the specification and grouping of the sensitivity analyses.

10.5.1 Switches in therapy and overlapping risk windows for all-cause TC

For the outcome of all-cause TC, a sensitivity analysis investigated the results of the primary association analyses after stratification by history of prior therapy with biologics. In DK, this analysis could not be presented due to masking rules (Table S1A.DK). In SE, the stratum with no biologic prior to therapy, crude and adjusted IRRs were attenuated toward 1.0; the stratum with one or more biologics prior to therapy, crude, DAG and fully adjusted IRRs were 1.4 (95% CI: 0.7, 2.7), 1.3 (95% CI: 0.6, 2.5) and 1.1 (95% CI: 0.6, 2.3), respectively. Crude and adjusted IRR-values remained very similar to those of the primary analysis and none of them were statistically significant regardless of the history of prior treatment with biologics in SE (Table S1A.SE).

A sensitivity analysis of GLM versus Other Anti-TNF for the all-cause TC outcome investigated whether the attribution of overlapping risk exclusively to previous therapy (not to the new therapy) would change the results and conclusions. In DK, the rather weak but statistically significant increased risk of GLM therapy observed in the primary analysis was reduced and became statistically insignificant for the crude IRR (1.2 (95% CI: 0.9, 1.6)), the DAG adjusted IRR (1.1 (95% CI: 0.8, 1.4)) and fully adjusted IRR (1.0 (95% CI: 0.8, 1.4)) (Table S1B.DK). In SE, the IRRs of the sensitivity analysis were slightly attenuated but similar to those of the primary analysis without significant increased risk for all-cause TC (Table S1B.SE).

Another analysis comparing GLM versus Other Anti-TNF for the all-cause TC outcome, evaluated the impact of a 90-days lag period between start of therapy and start of exposure. The results in both DK and SE were similar to those of the primary analyses (Tables S1C.DK and S1C.SE).

10.5.2 Misclassification of UC diagnosis

A sensitivity analysis investigated the effect of changing the operational diagnostic criteria of UC from one to two independent registrations of UC as primary discharge diagnosis, combined with having no registered diagnosis of CD. The results concerning CRC as the outcome could not be shown due to masking rules. For all-cause TC as the outcome, the slightly increased but statistically significant IRR-values found in DK when comparing GLM with Other Anti-TNF

were reduced and became statistically not significant; results for the comparison between GLM and TP were virtually unchanged from the primary analysis (Tables S2.DK). The results of the sensitivity analysis were similar to those of the primary analysis in SE (Table S2.SE).

10.5.3 Misclassification of exposure due to use of high level therapy codes (DK only)

A sensitivity analysis only performed in DK excluded patients with at least one high-level code used for registrations of therapies, reflecting incomplete specification of therapy in such instances. The result of this sensitivity analysis was similar to the the result of the primary analysis (Table S3.DK). Since high-level codes were not used in SE, this sensitivity analysis was relevant only for DK.

10.5.4 Risk windows for attribution of CRC

For CRC as the outcome, results of the sensitivity analyses with alternative definitions of risk windows were not presented due to masking rules. This related to scenarios where TP therapy contributed to overlap risk windows (Tables S4.DK and S4.SE); exposure started 6 months after commenced therapy and was ended 6 months after discontinued therapy (Tables S5A.DK and S5A.SE) or ended 2 years after therapy (Tables S5B.DK and S5B.SE).

10.5.5 Censoring for all-cause TC for attribution of CRC

For CRC as the outcome, the results of the sensitivity analyses with changing censoring criteria could not be presented due to masking rules. This observation related to the scenario where any type of colectomy (partial or TC) was used as a censoring event (Tables S6.DK and S6.SE).

10.5.6 Risk windows for attribution of all-cause TC

Increasing the length of the extended risk window to 6 months for all-cause TC as the outcome, gave results similar to those of the primary analysis in both the DK and SE populations (Tables S7A.DK and S7A.SE).

In a sensitivity analysis, the risk window for the TP cohort only was changed to start 90 days after first exposure and end 90 days after the last therapy or until one of the general triggers for end of follow. In this analysis, the risk was increased for GLM compared with TP in both the crude and the adjusted IRR values and for both DK and SE (Table S7B.DK and S7B.SE). In DK the fully adjusted IRR increased from 12.7 (95% CI: 8.1, 19.8) in the primary analysis to 18.8 (95% CI: 10.5, 33.5) in the sensitivity analysis. In SE, the corresponding increase was from 3.9 (95% CI: 2.3, 6.4) to 4.7 (95% CI: 2.7, 7.9), respectively.

For all-cause TC as the outcome, a scenario was established following the principle ‘once exposed – always exposed’. In DK, the adjusted IRR-values for the comparison between GLM and Other Anti-TNF became statistically insignificant whereas the both crude and adjusted

estimates for the comparison between GLM and TP remained virtually unchanged (Table S7C.DK). In SE, the results of the primary analysis were virtually unchanged for both comparisons in the sensitivity analysis (Table S7C.SE).

10.5.7 Competing risks for attribution of CRC

Since the study had CRC and all-cause TC as separate outcomes, a situation with possible competing risks was created: TC competes with CRC as an outcome at the same time as TC is a censoring event when assessing the risk of developing CRC, and colectomy due to CRC censors the risk of having a TC later. Furthermore, CRC, regardless of treatment, is associated with increased mortality which affects the risk of a later TC. Accordingly, it was justified to analyze the associations using a composite outcome of all-cause TC, CRC or death (yes/no).

It was planned to show the cumulative survival from the first entry to the therapy cohort using the dichotomous composite outcome. Note that the same patient may be represented in more than one therapy category depending on cohort membership and that the 90-days extended risk windows have not been applied. Since masking rules prevented showing Kaplan-Meier plots, the underlying cumulative data has been shown (Figures S1.DK and S1.SE). It has, however, been possible to estimate the crude IR of the composite outcome that represents the hazard underlying the Kaplan-Meier plots. In DK, the IR (per 1, 000 PY) was highest for the GLM cohort (63.4 (95% CI: 52.9, 75.5)) and lower for the Other Anti-TNF cohort (51.6 (95% CI: 47.8, 55.6)) where the IR for the TP cohort was substantially lower (26.6 (95% CI: 23.6, 30.0)). The same pattern was seen in SE but at generally lower levels; thus, for the GLM cohort, the IR for the composite outcome was 40.3 (95% CI: 29.5, 53.8), followed by 34.1 (95% CI: 30.6, 37.9) for the Other Anti-TNF cohort and 20.4 (95% CI: 18.4, 22.5) for the TP cohort.

For CRC as the outcome, no sensitivity analyses could be presented because it was not permitted to present the results due to masking rules of the primary association analyses. This was the case for an analysis of whether or not to apply all-cause TC as a censoring event for analysis with CRC as the outcome (Tables S8.DK and S8.SE).

Tables S9.DK and S9.SE show the association analysis using the composite outcome, together with the corresponding IRs of outcome in the categories by therapy. To reflect as closely as possible the primary association analyses, the 90-days risk window was applied in this sensitivity analysis. In DK, the crude IRR for the comparison between GLM and Other Anti-TNF was small but statistically significantly increased (IRR at 1.4 (95% CI: 1.1, 1.8)) but the adjusted IRR-values were attenuated and statistically insignificant (IRR at 1.2 (95% CI: 0.9, 1.6)) for both DAG adjusted and fully adjusted models. For the comparison between GLM and TP, the crude IRR was 5.7 (95% CI: 4.0, 8.2) which was increased to 8.0 (95% CI: 5.5, 11.6) in the DAG adjustment and 7.7 (95% CI: 5.3, 11.2) in the fully adjusted analysis. In SE, both the crude and the adjusted IRRs for the comparison between GLM and Other Anti-TNF were small and not statistically significant, and the adjusted IRR-values were further attenuated toward the null; for the comparison between GLM and TP the adjusted IRR-values were slightly lower than the crude value, but all IRR-values were statistically significantly increased.

10.5.8 Competing risks for attribution of all-cause TC

To assess effect of competing risk, it was the initial plan in protocol/SAP to investigate the effect of not using CRC as a censoring event for the risk of all-cause TC in a sensitivity analysis. However, since the primary analysis did not specify CRC as such a censoring event, the sensitivity analysis alternatively investigated the effect of using CRC as a censoring effect in the risk of all-cause TC. In both DK and SE and for both the comparisons of GLM versus Other Anti-TNF and GLM versus TP, the results of the sensitivity analysis were similar to the primary analysis (Tables S10.DK and S10.SE).

10.5.9 Missing information on the maximum extent of UC

The group of ICD-10 codes related to UC includes sub-codes for the specification of the extent of disease; the use of these sub-codes is not mandatory and UC codes unspecific for the extent occur. A pair of sensitivity analyses were performed in which all patients without any UC code specifying extent first, were assigned the class with maximal extent of UC and, second, assigned to the class with minimal extent of UC.

The results of the sensitivity analyses when assigning maximal and minimal extent of UC to patients with unknown status was similar to the results of the primary analyses. This applied to the comparisons between GLM and Other Anti-TNF as well as between GLM and TP, and for both DK and SE (Tables S11A-B.DK and S11A-B.SE).

10.5.10 Biologic therapies not included as study therapies

A sensitivity analysis investigated the effect of excluding all patients with a prior history of therapy with biologics other than the biologic study therapies (GLM, IFX or ADA). The results concerning CRC as the outcome could not be presented. For all-cause TC as the outcome, the slight but statistically significant IRR-values found in DK when comparing GLM with Other Anti-TNF were reduced and became statistically insignificant; results for the comparison between GLM and TP were virtually unchanged from the primary analysis (Table S12.DK). The Swedish results of the sensitivity analysis were similar to those of the primary analysis (Table S12.SE).

10.5.11 History of TP therapy in the GLM cohort

A sensitivity analysis restricted the GLM cohort to patients who were TP naïve at therapy cohort entry in the comparison between GLM and TP. The results concerning CRC as the outcome were not presented. For all-cause TC as the outcome, the strongly increased risk for GLM therapy versus TP observed in the primary analysis in DK was somewhat reduced but remained statistically significant in the sensitivity analysis. The crude IRR was reduced from 10.4 to 8.3; the DAG adjusted IRR from 13.6 to 12.1; the fully adjusted IRR was reduced from

12.7 to 9.9 (Tables S13.DK). The results for SE were inconclusive because of lack of observations for GLM therapy (Table S13.SE).

10.5.12 Validation of ascertainment sources for incident CRC (SE only)

The study ascertained incident cases of CRC from discharge diagnoses in the patient registers and not from cancer registry data. It was decided to perform a capture-recapture analysis comparing the results when also introducing the nation-specific cancer registries as an ascertainment source. In DK, the registration of a cancer-specific discharge diagnosis is fed directly into the Danish Cancer Registry. Since this high correlation between the two ascertainment sources in Denmark violates the assumptions underlying the capture-recapture analysis, this part of the sensitivity analysis was only performed for the SE data. For both DK and SE, the primary analyses with CRC as the outcome were performed using exclusively incident cases of CRC ascertained from the cancer registry data.

Table S14A.SE. shows the results of the capture-recapture analysis of the Swedish data. Due to masking rules, the full analysis could not be shown but from the available results, it was evident that a substantial number of incident cases were ascertained from discharge diagnoses in the patient register without being captured in the Swedish Cancer Registry.

The results of the sensitivity analysis using incident cases exclusively ascertained by the cancer registry data could not be shown for SE due to masking rules (Table S14B.SE). For the Danish data the full analysis could not be shown due to masking rules, but it was permissible to show incident numbers and corresponding PY at risk for therapy with Other Anti-TNF and TP, respectively. For both therapy categories, the IR of CRC was estimated at about 1 per 1,000 PY (Table S14B.DK).

10.5.13 Operational definition of all-cause TC as outcome

The initial study protocol specified TC due to intractable disease as an outcome. However, the outcome was eventually changed to all-cause TC since the automated data does not contain the reason for the TC. If this surgical procedure is not performed due to intractable inflammatory disease, CRC is assumed to be the most common alternative reason even though other forms of colectomy than TC typically will be used for CRC. Although reasons for performing a surgical procedure are not explicitly registered in the automated data, indirect evidence may be obtained from the discharge diagnoses registered in connection with the surgical procedure. Therefore, a sensitivity analysis was carried out with exclusion of all-cause total colectomies performed where CRC was registered as the main discharge diagnoses, It was assumed that the remaining all-cause total colectomies were assumed to be performed due to intractable UC.

For both DK and SE and for both the comparisons between GLM and Other Anti-TNF and between GLM and TP, the results of excluding colectomies with CRC as an underlying discharge diagnosis were similar to those of the primary analysis (Tables S15A.DK and S15A.SE).

Even though total colectomies have specific codes in the Nordic patient registers, coding practices may differ between surgeons and departments as well as over calendar time. This is particularly the case if the TC was performed as the final result of sequential but independently registered procedures. Therefore, a sensitivity analysis was performed in which the outcome was defined as any form of colectomy being coded as TC or other forms of colectomy.

The effect of accepting any type of colectomy as a relevant outcome is shown in Tables S15B.DK and S15B.SE. In DK, for the comparison between GLM and Other Anti-TNF the adjusted IRR-values were slightly reduced and became statistically insignificant; for the comparison between GLM and TP all IRR-values were lower than in the primary analysis but remained statistically significant (Tables S15B.DK). In SE, for the comparisons between GLM and Other Anti-TNF and between GLM and TP, the results of the sensitivity analysis were similar to those of the primary analysis (Table S15B.SE).

10.5.14 Risk windows without exposure to study therapies

An analysis investigated the consequences of ignoring all-cause total colectomies occurring outside risk windows representing exposure to the therapies under study. There were marked differences between DK and SE. In DK, the IRs within versus outside a 90-days risk window changes for GLM (incl. overlap), Other Anti-TNF and TP from 50.4 (95% CI: 40.8, 62.4) to 31.1 (95% CI: 21.8, 44.5); from 52.6 (95% CI: 48.0, 57.6) to 22.3 (95% CI: 18.7, 26.6); and from 23.9 (95% CI: 20.3, 28.2) to 11.0 (95% CI: 8.3, 14.7), respectively (Table S16.DK). In SE, the IRs within versus outside a 90-days risk window changes for GLM (incl. overlap), Other Anti-TNF and TP from 28.1 (95% CI: 18.5, 42.7) to 31.3 (95% CI: 20.0, 49.1); from 23.1 (95% CI: 19.9, 26.8) to 28.0 (95% CI: 23.5, 33.3); and from 12.4 (95% CI: 10.6, 14.6) to 16.5 (95% CI: 13.6, 19.9), respectively (Table S16.SE).

10.5.15 Timing of all-cause TC in relation to switching therapies

A sensitivity analysis investigated the effect modification by time period concerning switch between therapies with GLM and Other Anti-TNF. The results could not be shown due to small numbers (Tables S17.DK and S17.SE).

10.5.16 Quantitative Bias Analysis (Sweden only)

A QBA was performed to investigate the impact of the well-known under-ascertainment of intraveneous infusions with therapy like IFX in the Swedish National Patient Register (see Section 9.9.4 and SAP, Annex 2). In the QBA, the comparison was GLM versus ADA for the all-cause TC outcome and unmeasured confounder was IFX.

The external input values to the QBA are shown in Table S18A.SE. Swedish data investigated in the IQVIA validation study report[24] (Annex 3) showed that the prevalence of prior IFX use is somewhat higher for GLM users than ADA users. Other external data[9,10] showed that IFX

use is associated with a higher odds ratio for colectomy. The combined evidence from these measures (that serve as bias parameters for the QBA) suggests a potential bias against GLM when comparing the effects of GLM and ADA on risk of colectomy in a situation where exposure to IFX is under-ascertained.

In the QBA, the IRR contrasting GLM and ADA with respect to all-cause TC as the outcome were estimated with and without adjustment for IFX as an unmeasured confounder (Table S18B.SE and Text Table 10). Without adjustment for covariates and the unmeasured IFX, the crude IRR obtained in the main study in SE was 1.6 (95% CI: 1.0, 2.5) with marginal statistical significance. When running the adjusted models in the main study, the covariates reflecting the extent of UC and prior history of biologic therapy resulted in a poor fit that seemed implausible, particularly in the fully adjusted model. Since it was judged to reflect overfitting due to a high number of covariates included compared with a limited number of outcomes, these two variables were ignored in the adjustment in the main study. In the DAG adjusted model, the IRR was reduced to 1.5 (95% CI: 0.9, 2.4) and further reduced to 1.4 (95% CI: 0.9, 2.2) in the full model. In the QBA accounting for the unmeasured confounding effect of IFX, the crude IRR was 1.1 (95% CI: 0.9, 1.4) which was similar to the results of the DAG adjusted analysis (IRR at 1.1 (95% CI: 0.9, 1.4)) and was further reduced to 1.0 (95% CI: 0.8, 1.3) in the full model. None of IRRs after QBA adjustment for confounding effect of IFX was statistically significant. This result suggested that the IRR for all-cause TC in the primary analysis of the association between GLM and Other Anti-TNF in the main study could be reduced by about 30% and attenuated toward the null if prior IFX exposure was completely ascertained in the data from SE.

Text Table 10. Quantitative Bias Analysis (QBA); Sweden only. Adjusting for unmeasured confounder of prior IFX exposure for outcome of all-cause TC (GLM vs ADA cohort).

				Main study			QBA		
Outcome: All-cause TC	**Number N**	**Person-years (PY[a])**	**IR (per 1,000 PY)**	**IRR Crude (95% CI)[b]**	**IRR Adjusted, DAG (95% CI)[b]**	**IRR Adjusted, FULL (95% CI)[b]**	**IRR Crude (95% CI)[c]**	**IRR Adjusted, DAG (95% CI)[c]**	**IRR Adjusted, FULL (95% CI)[c]**
Treatment: GLM versus ADA									
GLM (incl. overlap with ADA)	21	548.9	38.3 (24.9, 58.7)	1.6 (1.0, 2.5)	1.5 (0.9, 2.4)	1.4 (0.9, 2.2)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.0 (0.8, 1.3)
ADA (ref.)	129	5,260.7	24.5 (20.6, 29.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: ADA: adalimumab; CI: confidence interval; DAG: directed acyclic diagrams; GLM: golimumab; IR: incidence rate; IRR: incidence rate ratio; PY: person-years; QBA: quantitative bias analysis; TC: total colectomy

[a] Person-years calculated as outlined in SAP Section 6.3.4 and Report Section 9.8.2, however ignoring IFX as an exposure.

[b] IRR_{obs}: Observed incidence rate ratio. Obtained from SE by rerunning the analysis for the outcome of all-cause TC comparing the GLM cohort and ADA cohort using the Poisson regression analysis, adjusting for multiple potential confounders available (see Table P2A.SE, the variables of extent of UC and history of prior biologic therapy were excluded) in the main study using the automated database (ignoring IFX as a confounder variable).

[c] IRR: Adjusted IRR and 95% simulation interval using the Lash method of probabilistic bias analysis.[32]

10.6 Adverse events/adverse reactions

This was a non-interventional database study based on secondary use of data prospectively collected for other purposes. No administration of any therapeutic or prophylactic agent was required in this protocol. No reporting of individual adverse events to regulatory agencies was planned for this database study due to lack of access to individual patient/subject records and because it was not possible to assess the causality of individual cases.

11 DISCUSSION

11.1 Key results

This observational study used nationwide routinely collected data from health registers in DK and SE to investigate whether GLM confers an increased risk of developing CRC and all-cause TC, respectively, compared with comparator therapies (Other Anti-TNF and TP) for patients with moderate to severe UC. The risk of HSTCL was included as an exploratory outcome. Patients were included during a period of seven consecutive years after the authorization of GLM on 18 September 2013 as a therapy for moderate to severe UC. Patients were followed after enrolment until 18 September 2021 and 31 December 2020 in DK and SE, respectively.

In addition to descriptive analyses, association analyses were performed using Poisson regression methods, with estimation of crude point estimates as well as estimates adjusted by a set of covariates established by clinical experts in a DAG process and a larger set of covariates in the fully adjusted model. A series of sensitivity analyses were performed.

In the study population of unique patients, the DK population was characterized by a relatively lower proportion of patients in the TP cohort (45%) compared with the SE population (69%). It was also found that the DK patients in the GLM and Other Anti-TNF cohorts had a lower frequency of history of prior therapy with TP (37%) compared with the corresponding SE patients (55%). Considered together, these findings might reflect a tendency to use biologics at an earlier stage in DK than in SE. Alternatively, the findings may partially reflect misclassification due to under-ascertainment of therapy with IFX in the Swedish National Patient Register. Otherwise, the distribution of demographic and clinical profiles was largely similar for the DK and SE patient populations.

No cases of HSTCL were identified, and this exploratory outcome was not analysed further.

Overall, the presentation of the results was challenged by small numbers of events for the CRC outcome. As required by GDPR, masking of results was done and the results of the association analyses for the CRC outcome could not be shown.

The data showed association measures for CRC outcome close to the unity value of 1 in both DK and SE for the comparison between GLM and Other Anti-TNF as well as for the comparison between GLM and TP, however, with wide 95% CIs. Furthermore, the IR of CRC in the therapy categories included in the analyses were similar to those of the total patient populations from the super cohorts in the DK (IR 1.2 per 1,000 PY) and SE (IR 1.5 per 1,000 PY). Considering these limitations, the study found no evidence of any association between study therapy and the risk of CRC.

For all-cause TC as the outcome, a slightly increased risk was seen for therapy with GLM compared to therapy with Other Anti-TNF. In the crude analyses, the association was statistically significant in DK (IRR 1.5 (95% CI: 1.2, 1.9)), but not statistically significant in SE (IRR 1.4 (95% CI: 0.9, 2.3)). In the adjusted analyses, IRR-values were attenuated. In DK, the IRR was 1.3 (95% CI: 1.0, 1.7) in the DAG adjusted analysis and 1.3 (95% CI: 1.0, 1.6) in the fully adjusted analysis. The corresponding adjusted IRRs in SE were 1.2 (95% CI: 0.7, 1.9) and 1.1 (95% CI: 0.7, 1.8), respectively. In the meta-analysis of aggregated data from DK and

SE, the weighted M-H estimate was statistically significant with an IRR of 1.5 (95% CI: 1.2, 1.8). There was no evidence of heterogeneity between DK and SE. The finding of a small increased risk of all-cause TC associated with GLM therapy may partly or wholly be explained by residual confounding by indication because direct measure of disease activity of UC prior to commencing therapy was not available and could only be captured using proxy variables. The meta-analysis did not adjust for any confounders and thus could be particularly prone to confounding by indication. Also, the GLM category included overlapping periods during which events were allocated to GLM, which could result in bias against GLM. Support for bias against GLM was found in the sensitivity analysis where overlapping exposure was attributed to the previous therapy rather than to GLM. In this sensitivity analysis, the IRRs were slightly reduced in SE (Table S1B.SE) while the IRRs in DK were reduced and became statistically insignificant (Table S1B.DK). For the Swedish part of the analysis, the QBA found evidence of bias against GLM due to the under-ascertainment of IFX therapy in the Swedish patient register.

A increased IRR of all-cause TC was seen in the comparison between GLM and TP therapies, particularly in DK. In the crude analyses, the association was statistically significant in both DK (IRR 10.4 (95% CI: 6.7, 16.0)) and SE (IRR 4.4 (95% CI: 2.7, 7.0)). In the adjusted analyses, IRR were 13.6 (95% CI: 8.7, 21.3) and 4.5 (95% CI: 2.7, 7.4) for DK and SE in the DAG adjusted analysis and 12.7 (95% CI: 8.1, 19.8) and 3.9 (95% CI: 2.3, 6.4), respectively, in the fully adjusted analysis. In the meta-analysis of aggregated data from SE and DK, the weighted M-H estimate obtained without adjustment for covariates was statistically significant with IRR 7.8 (95% CI: 5.7, 10.9), and there was statistically significant evidence of a high level of heterogeneity between the countries.

According to the clinical experts associated with this study, GLM probably represents second or even third line therapy whereas TP is expected to be administered to UC patients with less severe disease as the first line therapy. This was supported by the study data shown in Table D2A.DK, Table D2A.SE, Table D2B.DK and Table D2B.SE. Therefore, the comparability between patients in GLM therapy versus patients treated with TP is compromised, and the increased risk of all-cause TC for GLM therapy compared with TP therapy may be explained by differences in disease activity and/or treatment resistence rather than caused by GLM therapy *per se*.

The IR of all-cause TC was approximately twice as high in DK (33.1 per 1,000 PY) as in SE (17.6 per 1,000 PY). However, the IR of all-cause TC associated with TP therapy in DK (7.6 (95% CI: 5.2, 11.1)) was similar to that in SE (8.8 (95% CI: 7.2, 10.8)), while the IRs of all-cause TC associated with GLM (79.0 (95% CI: 63.8, 97.7)) and Other Anti-TNF (53.6 (95% CI: 48.7, 59.1)) in DK were higher than those (38.5 (95% CI: 25.1, 59.0) and 26.6 (95% CI: 22.8, 31.0), respectively) in SE (Text Table 9B). Together these findings suggest that the difference in colectomy rates is restricted to patients on biologic therapy. Since the patients on biologic therapy represent a small proportion of the total population of patients with UC, the IR of all-cause TC in the total patient population may be at the similar level in the two countries as also found in a recent study.[19] In a study using data from Danish National Patient Register, it was reported that the 5-year cumulative probability of first major surgery in UC was 7.5%;

9-year cumulative probability was 9.1% in 2003-2011 in DK.[35] In a population-based cohort study of UC patients in SE during 2005–2009, five years after diagnosis of UC, 5.3% of patients had colectomy.[36]

These findings must be interpreted in light of the fact that the DK population had a much lower proportion of patients in the TP cohort (45%) than the SE population (69%), see Text Table 6A. Even though part of this difference may be explained by the under-ascertainment of IFX therapy in the SE data, the difference in the absolute number of members of the TP cohort between DK and SE is larger than explainable by demographical factors in the patient populations. According to the clinical experts associated with the present study, it is generally believed that patients with UC in DK are treated in accordance with similar guidelines and in healthcare systems that are comparable in terms of equal access to similar health services. The findings of the present study suggest that for the segment of patients with moderate to severe UC, patients in DK (when compared with patients in SE) tend to be treated less frequently with TP before advancing to biologic therapy, and also have a higher rate of all-cause TC once biologic therapy has commenced. The lack of pathology diagnoses informing of pre-malignancies like high grade dysplasia as well as the lack of information on reasons for performing an all-cause TC limit further investigation of these findings by means of data in the present study.

The findings of associations between all-cause TC and study therapies remained largely unchanged in the various sensitivity analyses with a few exceptions. The QBA performed to adjust for under-ascertainment of IFX in the data from SE showed the risk of all-cause TC for GLM vs. ADA therapies were about 30% reduced after QBA adjustment for prior IFX exposure, and the QBA adjusted IRRs were not significantly different from 1. Accordingly, there was some degree of bias against GLM due to the under-reporting of IFX exposure in SE when evaluating the risk of all-cause TC comparing GLM with Other Anti-TNF (combining ADA and IFX therapies), and the IRRs could be further attenuated if complete prior IFX exposure could be obtained and adjusted in the primary analysis of the association between GLM and Other Anti-TNF in SE.

11.2 Limitations

Overall, it is considered a major limitation in this study that, due to nationally implemented regulations as a consequence of GDPR, it was not possible to present in detail and discuss the results of analyses based on small sub-samples of the study population.

Specific aspects of limitations are summarized below.

Ascertainment of patients with UC

- It was assumed that the patients with UC requiring the therapies of relevance for this study were ascertained with a very high level of completeness from the hospital activity and prescription registrations systems. However, because IBD phenotype may change before, as well as after, the first registered activity with UC as the primary diagnosis, patients registered with a UC diagnosis may also have been registered with encounters where CD had been recorded as a diagnosis. Patients who had received both diagnoses

were included in the study base only to the extent that UC is the main diagnosis registered prior to enrolment in the initial therapy cohorts. To address this concern further, a sensitivity analysis was carried out that included two independent registrations of an UC diagnosis as well as no registered CD diagnosis. The association with all-cause TC when comparing GLM with Other Anti-TNF in both DK and SE were somewhat reduced.

Capturing information on treatment, changes in treatment and exposure windows

- The protocol for this study was based on the therapeutic landscape in 2014. Later in 2014 vedolizumab was approved as a biologic therapy for moderate to severe UC. Therefore, vedolizumab therapy was not managed as a separate exposure category in this study, but was included as a covariate together with other biologics not included as study therapy. Because of the limited use of vedolizumab during the study period, it is judged that the results have not been distorted due to the lack of managing treatment with vedolizumab as a separate exposure category. Tofacitinib and ustekinumab received European marketing authorization in 2018 and 2019, respectively, and more recently upadicitinib and ozanimod have also received authorization. All these drugs were approved too late to have been otherwise incorporated into the study design.
- The study was not designed to evaluate the effect of GLM dosing. Evidence from the PURSUIT clinical development program for GLM in UC has shown that almost one third of patients with an inadequate response to the usual GLM induction dosing regimen will achieve a response if a dose 100 mg q4w (instead of the usual 50 mg q4w) is given. This early dose optimization (for patients <80 kg) was approved by EMA in September 2018, at a time when the study was well underway. Considering that dose optimization is important to ensure continued clinical response, and thus avoid relapses and colectomies later on, this could have biased the results against GLM.[37,38,39]
- In DK, errors or nonspecific coding of relevant therapies may cause exposure misclassification and inappropriate exclusion from the study if treatment with biologic agents is coded at high-order level rather than the detailed level where the specific drug is identified. A sensitivity analysis addressing this issue found no evidence that the occurrence of high-level codes would distort the results.
- Ascertainment of hospital-based IFX infusions are expected to be under-ascertained in automated Swedish registry data. To the extent that prior use of IFX is a marker of a higher risk of all-cause TC, missing information on IFX exposure could confound the association between GLM and all-cause TC if prevalence of prior IFX exposure varied by GLM vs ADA exposure. A probabilistic QBA carried out specifically to address this issue showed that the IRRs of all-cause TC were reduced about 30% after QBA adjustment for prior IFX exposure. The QBA-adjusted IRRs were not stiatistically significantly different from 1. Thus, the under-reporting of IFX therapy in SE was likely to induce some degree of bias in the comparison of risk of all-cause TC between GLM and Other Anti-TNF that combined ADA and IFX therapies in the primary association analysis in SE.

- Study therapies may have been used for CD or for dermatological and rheumatologic indications. Therefore, patients may have been exposed to these therapies before the first registration of UC (or CD), and the same therapy may have been administered under different indications over time for the same patient. For this study protocol, study drugs were included regardless of underlying indication. However, patients needed to have at least one main diagnosis of UC prior to entry to the initial therapy cohort. The potential bias due to such sources should have been handled by inclusion of relevant covariates and performing sensitivity analyses, which showed no evidence of distortion of the results due to such bias.
- Assuming there is an effect of study drugs on the outcomes of interest, the true biologic risk window is not known for the outcome of CRC. Our primary analyses for this outcome assumed that for biologics, the risk window is "once exposed, always at risk". Sensitivity analyses exploring the effect of alternative risk window definitions revealed no evidence of distortion of results due to such alternatives.
- Similar to CRC, the true risk window for all-cause TC is not known. The primary analysis for this outcome used a 90-days risk window. In sensitivity analyses using alternative risk window definitions there were no evidence of distortion of results.
- The commencement of a new therapy may be established from the first time the therapy is registered. In contrast, the discontinuation of a therapy is not registered explicitly in the automated data but must be inferred by cease of registration of the therapy concerned. For the same reason it is difficult to distinguish between switch of therapies (crossover) versus discontinuation and later re-uptake of therapy after a period without therapy, making it difficult to tease out the effect of individual specific therapies. This is considered a major limitation that applies to pharmaco-epidemiological observational studies in general. In the present study, relatively few patients were registered with more than one therapy during the study period; however, many of these patients had complex treatment trajectories, with many shifts and even commencement of competing therapies registered on the same day. As stated above, sensitivity analyses using alternative risk window definitions in various scenarios provided no evidence of distortion of results.
- Therapy offered as part of participation in a controlled clinical trial was not captured by means of the available data sources. Based on enquiries made to clinical experts when preparing the present study it was concluded that during the time span covered by the study only very few study persons might have been enrolled in trials. Therefore, this source of under-ascertainment was considered to have negligible effect on the results.

Capturing information on outcomes

- In DK, the registration of new cases of CRC may be considered virtually complete in the Danish setting due to a tight coupling between diagnostic activities and diagnosis entered into the National Patient Register and the input to the Danish Cancer Registry. In SE, however, incomplete ascertainment of new cases of CRC may be found. Due to

latency when reporting to the national cancer registries, the study relied on hospital discharge diagnoses as the main source of CRC information. For the data from SE, a formal capture-recapture analysis was established to validate case ascertainment. Due to small numbers of outcomes masking must be made without the possibility to show the detailed results. However, the data showed a substantial under-estimation of new cases of CRC in the Swedish Cancer Registry. Since the study relied on hospital-based ascertainment of CRC cases, the effect of under-ascertainment in the Swedish Cancer Registry was considered of no importance for the association analyses with CRC as the outcome.

- In general, errors and inappropriate coding of surgical procedures in the central health registries may cause deficits or misclassifications in the identification of outcomes. In DK, however, the PPV of all-cause TC using national registry data, validated against clinical records, was shown to be high.[11] This was also found to be the case for ascertainment of all-cause TC using the Swedish register data in the separate validation study performed by IQVIA (see Annex 3).
- HSTCL was an explorative outcome in the study. As a consequence of its rarity, no incident cases of HSTCL were registered and, accordingly, none of the planned analyses could be performed for this outcome.

Information on covariates

- Specific information on disease activity of UC and variations over time for the individual patients was not available but had, to the extent possible, to be ascertained by proxies from the automated data (number of colonoscopies and flexible sigmoidoscopies within one year prior to cohort entry; ≥2 courses of systemic steroid use in prior 12 months of therapy cohort entry; history of therapy with TP; history of therapy with biologics). It is possible that these proxies individually or taken together may not have adjusted sufficiently in the association analyses. This would induce residual 'confounding by indication'.
- Information on extent of UC was inferred from the ICD-10 codes registered as activity diagnosis for hospital encounters. Accordingly, the validity of this information depends on the level of details used in daily coding practice. As assessed in sensitivity analyses, the impact of missing information on extent of UC was limited.
- The time window concerning availability of information on history of therapies has varied between registers and between DK and SE. However, from year 2005 onwards drug use as captured from prescription registers and hospital administered therapies as captured from hospital activity registrations were available on equal terms in both DK and SE. This was considered satisfactory for the purpose of the present study.
- During the analysis, a change was made to the update of covariates used in multivariable modeling. Rather than values of covariates measured at the time of therapy start or therapy switch, covariates were updated daily up until the outcome or censoring event. This was done in order to capture updating of time-varying covariates like age and disease duration equally between patients during periods without changing

therapy since the maximal length of such periods differed between patients depending on when they were enrolled in the first therapy cohort. By using covariate values measured after the start of therapy, bias due to residual confounding by indication could have been introduced, as the analysis may not have adjusted completely for factors influencing the therapy decision. In particular, multivariable modeling analyses were not able to adequately account for biologic use occurring prior to start of treatment with GLM or Other Anti-TNF, which was imbalanced between these cohorts at baseline (Tables D2A.DK and D2A.SE) and is considered an important confounder as it can reflect underlying disease activity. Additionally, adjustment for covariates measured after therapy could have introduced collider stratification bias, which can arise from conditioning on an intermediate in the causal pathway.[40] This might be the case for the covariate representing prior TP therapy. However, for the other time-varying covariates including age, disease duration and calender time, such time-dependent bias seems unlikely.

- In the meta-analysis of weighted effect estimates from DK and SE, no statistical software was identified that could apply M-H methodology to aggregated person-time data at the the same time as offering both a quantative assessment of heterogeneity between DK and SE and the inclusion of covariates in the analysis. It was justified to select an analytic approach (the function rma.mh in the package metafor included in the R package) including a quantative assessment of heterogeneity, since the inclusion of covariates was restricted to only one in compliance with the GDPR guidelines. It must be stressed that the measure of heterogeneity (the I^2-value) is considered to be prone to bias when the number of included studies is small.[34]

11.3 Interpretation

The use of automated data, collected for other purposes in nationwide health registers in DK and SE, adds to the validity of the results because data are produced independently of the study. A high level of validity is further supported by the results being unaffected by adjustments made in the analyses.

Interpretation is challenged by the need to mask key results due to small numbers of outcomes and observations, particularly for the CRC outcome. Upon inspection of the underlying results, no evidence of any associations between therapy and the risk of CRC was found with any of the study therapies.

In the study population of unique patients, the DK population was characterized by a relatively lower proportion of patients in the TP cohort compared with the SE population. Patients in the GLM and Other Anti-TNF cohorts in DK also had a lower prevalence of prior TP therapy compared with these cohorts in SE. Considered together, these findings might reflect a tendency to use biologics at an earlier stage in DK than in SE. Alternatively, the findings may wholly or partly reflect a selection bias due to under-ascertainment of therapy with IFX in the Swedish National Patient Register.

In terms of differences of patient characteristics at therapy cohort entry, GLM cohort tended to have a longer duration of UC and a higher proportion of prior use of biologics than the Other Anti-TNF cohort, suggesting that GLM may have been used preferentially after a course of another biologic. Compared to the TP cohort, which is naïve both to prior TP and to prior biologics, GLM cohort had a higher proportion of prior use of biologics and prior use of TP therapy and a longer duration of UC.

Overall data suggest a slightly increased risk of all-cause TC when comparing GLM with Other Anti-TNF therapies. This finding was particularly noteworthy in DK and should be interpreted in conjunction with other study findings. First, 89% GLM patients in DK (60% in SE) were previously treated with biologics at therapy cohort entry, while only 9% of Other Anti-TNF patients in DK (5% in SE) were previously treated with a biologic at cohort entry. These differences suggest that more GLM patients were already on second or third line therapy and had more disease activity and higher risk of colectomy than Other Anti-TNF patients at cohort entry. This is consistent with the Taxonera study[9] that showed a much higher incidence of colectomy with second or third line of therapy of GLM. Second, the overlap period was grouped with GLM after therapy switch due to small numbers. When patients had worsening disease or lost response to current therapy, they would switch therapy. This is the time associated with higher disease activity, thus higher risk of colectomy. Thus, grouping the overlapping period with GLM therapy could result in bias against GLM. The sensitivity analysis that allocated the overlap period to the previous therapy, rather than the new therapy, eliminated the slightly higher risk of colectomy in DK and further supports a bias against GLM when grouping the overlapping period exclusively to GLM therapy. Third, there was no direct measure of disease activity in this study and only a few proxy variables were available which may not accurately reflect disease activity. Thus, disease activity may not have been adjusted sufficiently in the association analyses. This would induce residual confounding by indication. In addition, under-reporting of prior IFX exposure in SE was likely to induce some degree of bias as shown in QBA. In summary, the slight increase in all-cause TC with GLM compared to Other Anti-TNF therapies may be due to bias and residual confounding. Another observational study similarly concluded that the apparent higher risk of colectomy was partially a result of study bias and confounding.[41]

Although an increased IRR of all-cause TC was observed in the comparison between GLM and TP therapy, particularly in DK, this increased IRR could be explained by a number of factors. First, in clinical practice, TP is typically administered to patients with mild disease before anti-TNF therapy. In contrast, anti-TNF is prescribed to patients with moderate to severe disease, and many patients commencing GLM therapy had already been treated with TP. Therefore, the patient populations are not comparable. Second, in this study 100% of TP patients were biologic naïve while only 11% of GLM patients in DK (40% in SE) were biologic naïve. GLM represents second or even third line therapy and is administered to patients with more severe disease, whereas TP is expected to be administered as first line therapy and to patients with less severe disease. Patients who advance to a third line therapy have already failed to achieve sustained remission with the first two therapies. As such, they are starting to run out of therapies and if another therapy fails to control symptoms, they may be more likely to require colectomy. Third, patients need to switch therapy when they lose response to TP or

another anti-TNF. This is the time when worsening disease or condition would likely prompt a colectomy, as opposed to the effect of the new therapy. In this study, the analysis attributed the overlapping risk period to GLM after TP patients switched to GLM, and also attributed the overlapping risk period with Other Anti-TNF to GLM (when comparing GLM with TP), both of which could result in bias against GLM. For these reasons, the observed increased risk of all-cause TC may reflect, wholly or partially, confounding by indication and analysis bias, rather than by GLM therapy per se. No causal relationship can be inferred from the results.

In this study, a doubling of the all-cause TC rate was observed in the DK population compared with the SE population for patients on biologic therapy (Table P2A.DK versus Table P2A.SE), whereas there was no statistically significant difference for patients on TP therapy (Table P2B.DK versus Table P2B.SE). This suggests that in DK, the risk of all-cause TC was doubled compared with SE for patients with more advanced disease, but not for patients with less severe disease. This was unexpected because, in general, the healthcare system and UC treatment guidelines should be very similar between DK and SE according to clinical experts. Furthermore, a recent Scandinavian study on CRC in UC found that the cumulative risk of colectomy during follow-up in UC patients was similar in DK and SE.[19] This study did not investigate all-cause TC rates specifically in relation to therapy with biologics, and it is possible that the segment of patients treated with biologics is too small to influence the results in the total population of UC patients.

11.4 Generalisability

The health registers in DK and SE used for this study cover the total respective populations and are in general assumed to be of high quality in terms of completeness and validity of the data.[22] Therefore, the results of the study are considered generally representative of populations that are comparable in the Nordic countries concerning health care systems and access to care.

The premise of generalization depends on comparability of patient populations. Therefore, when generalizing the results from the present study, specific considerations must be made concerning the extent to which treatment patterns are comparable across patient populations with assumed moderate to severe UC.

12 OTHER INFORMATION

N.A.

13 CONCLUSION

This Nordic PASS study (MK8259-013) was an observational cohort study of patients with moderate to severe UC performed in DK and SE based on nationwide health registers that in general are considered of high validity concerning completeness in ascertainment of exposures and outcomes. Exposure to GLM was compared to exposure with Other Anti-TNF therapies (IFX and ADA grouped into one category) and with TP concerning the development of incident CRC and incident all-cause TC. The development of incident HSTCL was an exploratory outcome.

Using Poisson regression analysis, and adjusting for a range of potential confounders, the study found no evidence that therapy with GLM conferred higher risk of developing CRC compared with Other Anti-TNF therapies approved for use in moderate to severe UC or compared with TP therapy. However, due to small numbers of outcomes in exposure categories the 95% CIs were large, and result details could not be shown due to GDPR regulations.

Using Poisson regression analysis, and adjusting for a range of potential confounders, the study found a slightly increased risk of all-cause TC for GLM compared with Other Anti-TNF therapies approved for use in moderate to severe UC, particularly in DK. It is possible that this finding may reflect a number of potential study biases, notably residual confounding by indication and inability to completely adjust for differences in disease activity.

Although the IRR of all-cause TC was several times higher for GLM compared with TP therapy, with the highest rate ratio in DK, the increased IRR of all-cause TC may wholly or partially be due to potential biases and residual confounding by indication. Patients on TP were not compatible with patients on GLM; thus, no causal relationship can be inferred.

Results from a range of sensitivity analyses with alternative specifications of patient characteristics, exposures and outcomes did not materially alter the findings of the primary analyses, with a few exceptions that either eliminated or reduced the risk of all-cause TC due to GLM.

No cases of HSTCL were registered, preventing further analyses. This finding confirmed that HSTCL has a low frequency in patients with moderate to severe UC.

Collectively, this study provided no evidence that GLM poses an increased risk of CRC or all-cause TC.

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15 ANNEX LIST

CCI

Annex 2 Result Tables and Figures

A. Descriptive analyses

B. Main association analyses

C. Sensitivity analyses

CCI

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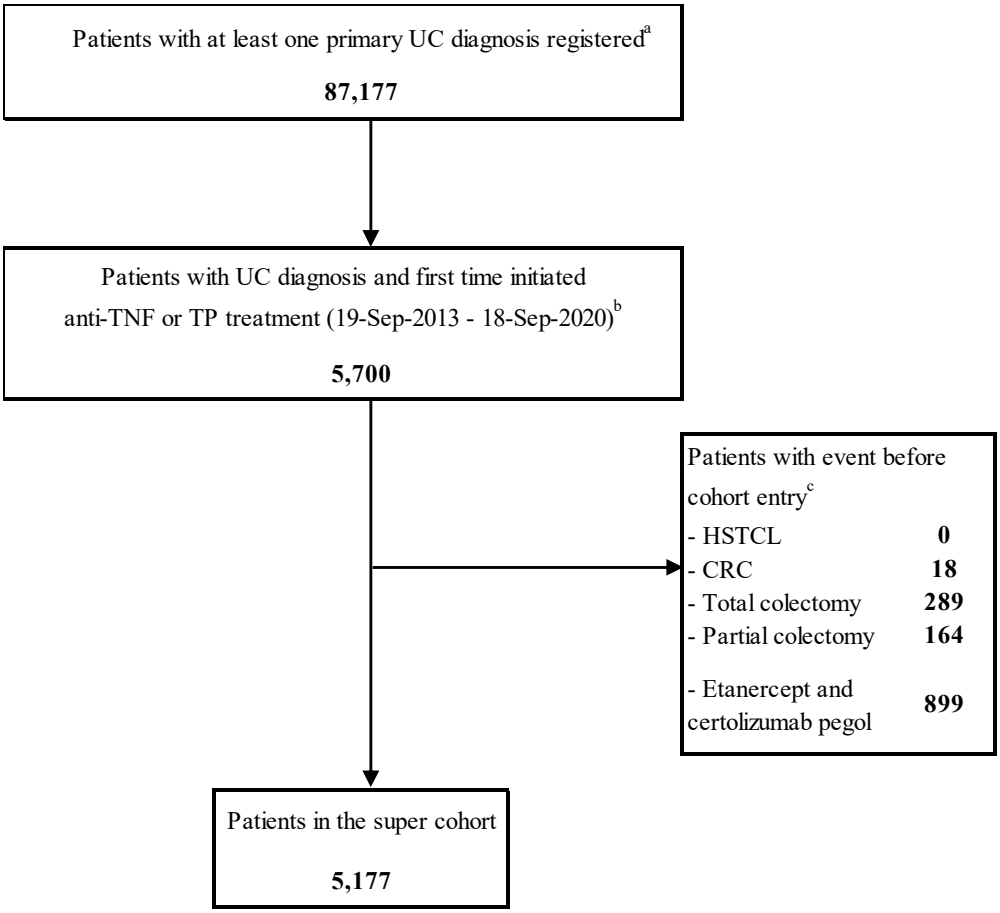
15.2 Annex 2 Result Tables and Figures

A. Descriptive analyses

Figure D1.DK Summary flow diagram of the establishment of population of unique study patients (the super cohort).



Abbreviations: CRC: colorectal cancer; HSTCL: hepatosplenic T-cell lymphoma; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis

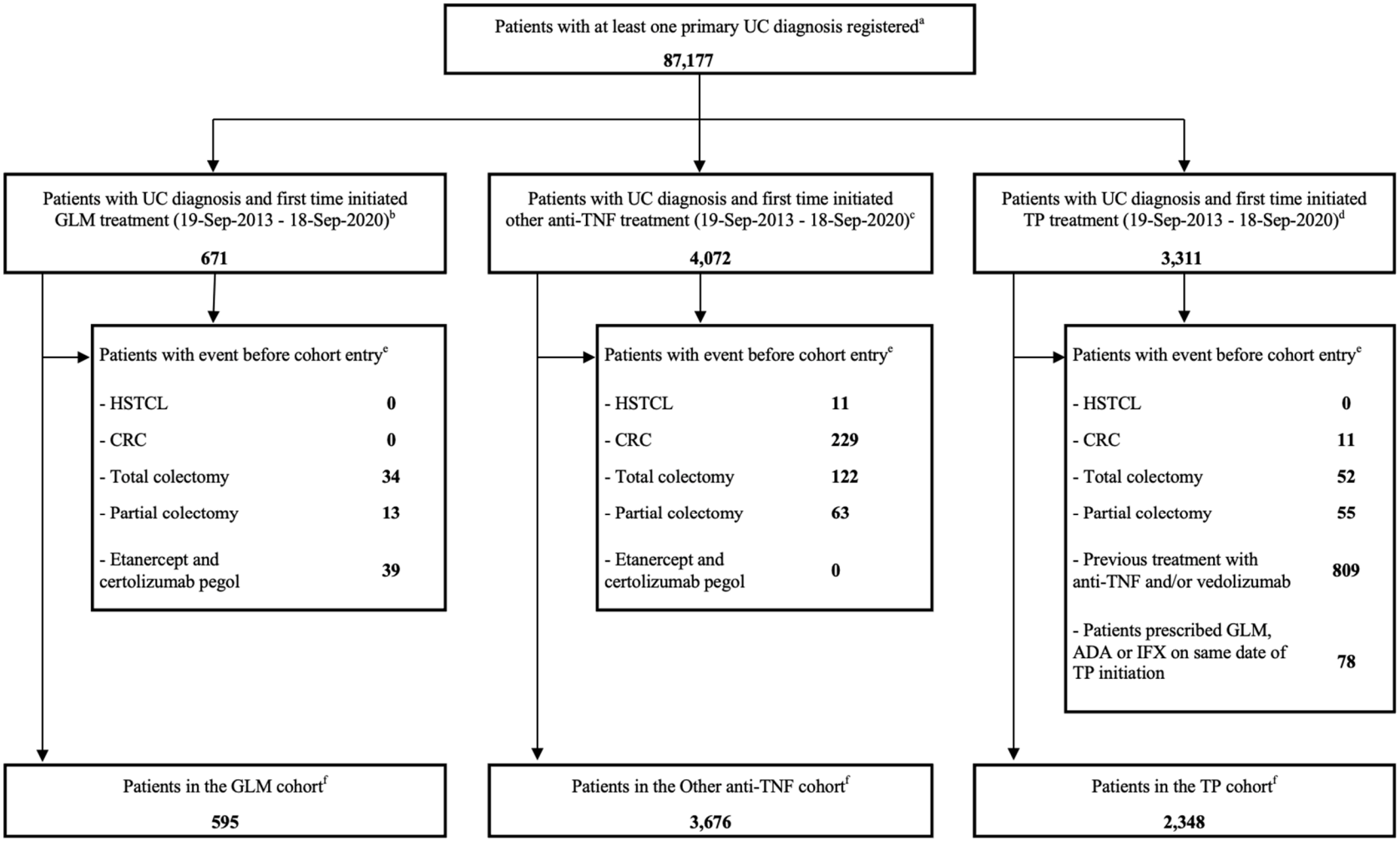
[a] Ascertainment is based on both inpatients and outpatient contacts registered in the National Patient Register until newest available data. Inclusion date of patients refers to "admission date" for inpatient for hospitalized patients and "date of first visit" for outpatient contacts

[b] UC must have been registered as the primary discharge diagnosis before or, at latest, at the event that qualifies for therapy cohort entry

The assignment to super cohort is determined by the first qualifying therapy occasion after 19 September 2013.

[c] A patient can have more than one of the exclusion criteria. The sum of exclusions can therefore exceed the number of patients excluded. Patients entering the cohort of TP therapy must be naïve to any anti-TNF and/or vedolizumab

Figure D2.DK Summary flow diagram of the establishment of therapy cohorts.



(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

Abbreviations: CRC: colorectal cancer; GLM: golimumab; HSTCL: hepatosplenic T-cell lymphoma; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis

[a] Ascertainment is based on both inpatient and outpatient contacts registered in the National Patient Register until newest available data. Inclusion date of patients refers to "admission date" for hospitalized patients and "date of first visit" for outpatient contacts
UC must have been registered as the primary discharge diagnosis before or, at latest, at the event that qualifies for therapy cohort entry.
For all three therapy cohorts, the assignment to therapy cohort is determined by the first qualifying therapy occasion after 19 September 2013

[b] The therapy cohort of UC patients treated with GLM (the GLM cohort) is defined as all patients who for the first time are registered with GLM from 19 September 2013. The patients in the GLM cohort can be former users of the Other Anti-TNF agents as well as TP. Last date of cohort entry: 18 September 2020.

[c] The therapy cohort of UC patients treated with IFX or ADA (Other Anti-TNF cohort) is defined as all patients who for the first time are registered with IFX or ADA from 19 September 2013. Hence, ADA users must be naïve to ADA and IFX users must be naïve to IFX but ADA users may have used IFX before, and IFX may have used ADA before. The patients in the Other Anti-TNF cohort can be former users of GLM as well as TP. Last date of cohort entry: 18 September 2020

[d] The therapy cohort of TP patients (the TP cohort) is defined as all patients who for the first time are registered with TP (ATC: *L01BB02* or *L04AX01*) from 19 September 2013. Users must be naïve to both TP, anti-TNF therapy and vedolizumab (ATC *L04AA33*). Last date of cohort entry: 18 September 2020

[e] A patient can have more than one of the exclusion criteria. The sum of exclusions can therefore exceed the number of patients excluded

[f] A patient can enter more than one cohort if qualification criteria for entering another cohort are met after entering a specific cohort. The flow chart accounts for all cohort entries which totals to more than the number of unique patients represented in all therapy cohorts grouped together

Table D1.DK Number of entries and duration of follow-up[a], by therapy cohorts and year of first-time entry to the therapy cohort.

Measures	Therapy cohort		
	GLM (N = 595)	**Other Anti-TNF (N = 3,676)**	**TP (N = 2,348)**
All study entry years, n	595	3,676	2,348
Person-years of follow-up[a]	2,405.8	15,532.1	10,994.8
Mean (SD)	4.0 (1.9)	4.2 (2.0)	4.7 (2.0)
Median (Q1, Q3)	3.9 (2.5, 5.5)	4.2 (2.5, 5.9)	4.8 (3.0, 6.5)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2013, n	<5	N.P.	N.P.
Person-years of follow-up[a]	N.P.	N.P.	N.P.
Mean (SD)	N.P.	N.P.	N.P.
Median (Q1, Q3)	N.P.	N.P.	N.P.
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2014, n	N.P.	N.P.	N.P.
Person-years of follow-up[a]	N.P.	N.P.	N.P.
Mean (SD)	N.P.	N.P.	N.P.
Median (Q1, Q3)	N.P.	N.P.	N.P.
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2015, n	58	480	375
Person-years of follow-up[a]	359.2	2,910.9	2,293.8
Mean (SD)	6.2 (0.3)	6.1 (0.8)	6.1 (0.7)
Median (Q1, Q3)	6.2 (5.9, 6.5)	6.1 (5.9, 6.4)	6.2 (6.0, 6.5)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2016, n	76	498	354
Person-years of follow-up[a]	390.8	2,574.0	1,832.2
Mean (SD)	5.1 (0.4)	5.2 (0.5)	5.2 (0.5)
Median (Q1, Q3)	5.2 (4.9, 5.4)	5.2 (5.0, 5.5)	5.2 (5.0, 5.5)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2017, n	110	568	327
Person-years of follow-up[a]	463.0	2,366.2	1,357.5
Mean (SD)	4.2 (0.3)	4.2 (0.5)	4.2 (0.5)
Median (Q1, Q3)	4.2 (3.9, 4.5)	4.2 (4.0, 4.5)	4.2 (3.9, 4.5)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2018, n	104	513	319
Person-years of follow-up[a]	329.2	1,624.3	1,020.1
Mean (SD)	3.2 (0.4)	3.2 (0.4)	3.2 (0.4)
Median (Q1, Q3)	3.2 (2.9, 3.4)	3.2 (2.9, 3.4)	3.2 (3.0, 3.5)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2019, n	106	583	281
Person-years of follow-up[a]	232.9	1,274.1	619.9
Mean (SD)	2.2 (0.3)	2.2 (0.4)	2.2 (0.3)
Median (Q1, Q3)	2.2 (2.0, 2.4)	2.2 (1.9, 2.5)	2.2 (1.9, 2.5)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2020, n[b]	63	447	188
Person-years of follow-up[a]	83.7	605.4	259.2
Mean (SD)	1.3 (0.2)	1.4 (0.2)	1.4 (0.2)

Measures	Therapy cohort		
	GLM (N = 595)	**Other Anti-TNF (N = 3,676)**	**TP (N = 2,348)**
Median (Q1, Q3)	1.3 (1.1, 1.5)	1.4 (1.2, 1.5)	1.4 (1.2, 1.6)
Min, Max	N.P.	N.P.	N.P.

Abbreviations: GLM: golimumab; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Note: For this table, duration of follow-up is based on the date of entry to a therapy cohort until the first event of death, emigration or end of data-collection (31 October 2021). Therapy cohort entries are not mutually exclusive. Thus, patients entering more than one therapy cohort will contribute follow-up time to each cohort

[b] Latest possible date of recruitment of new study persons is 18 September 2020, but switches to other therapy cohorts may take place until 18 September 2021)

Table D2A.DK Demographic and clinical characteristics of unique patients distributed by initial therapy cohorts.

Characteristic	Initial therapy cohort		
	GLM (N = 199)	Other Anti-TNF (N = 2,630)	TP (N = 2,348)
Age at cohort entry (in years)			
Mean (SD)	44.6 (14.9)	39.7 (16.8)	41.4 (18.8)
Median (Q1, Q3)	42.5 (33.9, 56.0)	37.4 (25.5, 51.7)	39.6 (25.8, 56.3)
Min, Max	N.P.	N.P.	N.P.
Age group in years, n (%)			
<35	56 (28.1)	1,194 (45.4)	1,011 (43.1)
≥35	143 (71.9)	1,436 (54.6)	1,337 (56.9)
Sex, n (%)			
Male	92 (46.2)	1,318 (50.1)	1,201 (51.1)
Female	107 (53.8)	1,312 (49.9)	1,147 (48.9)
Calendar year of cohort entry, n (%)			
2013	<5	N.P.	N.P.
2014	N.P.	N.P.	N.P.
2015	22 (11.1)	329 (12.5)	375 (16.0)
2016	21 (10.6)	337 (12.8)	354 (15.1)
2017	27 (13.6)	412 (15.7)	327 (13.9)
2018	28 (14.1)	336 (12.8)	319 (13.6)
2019	31 (15.6)	414 (15.7)	281 (12.0)
2020	16 (8.0)	318 (12.1)	188 (8.0)
UC duration (time since first registration of primary UC) in years			
<1	11 (5.5)	937 (35.6)	970 (41.3)
1-4	33 (16.6)	598 (22.7)	705 (30.0)
5-9	57 (28.6)	413 (15.7)	275 (11.7)
≥10	98 (49.2)	682 (25.9)	398 (17.0)
Maximum extent of disease before or same date as cohort entry, n (%)			

Characteristic	Initial therapy cohort		
	GLM (N = 199)	**Other Anti-TNF (N = 2,630)**	**TP (N = 2,348)**
E1: Ulcerative proctitis	8 (4.0)	127 (4.8)	120 (5.1)
E2: Left sided UC (distal UC)	13 (6.5)	184 (7.0)	312 (13.3)
E3: Extensive UC (pancolitis)	163 (81.9)	1,903 (72.4)	1,502 (64.0)
Unclassifiable extent	15 (7.5)	416 (15.8)	414 (17.6)
Received at least 2 UC primary diagnoses on or before date of cohort entry, n (%)	No: 24 (12.1)	No: 433 (16.5)	No: 500 (21.3)
	Yes: 175 (87.9)	Yes: 2,197 (83.5)	Yes: 1,848 (78.7)
At least 2 therapys with systemic steroid, ≤1 year before cohort entry, n (%)	No: 113 (56.8)	No: 1,340 (51.0)	No: 844 (35.9)
	Yes: 86 (43.2)	Yes: 1,290 (49.0)	Yes: 1,504 (64.1)
Prior therapy with ciclosporine, ≤1 year before cohort entry, n (%)	No: 199 (100.0)	No: N.P.	No: N.P.
	Yes: 0 (0.0)	Yes: N.P.	Yes: <5
Prior diagnosis (primary or secondary diagnosis) before cohort entry with			
Sclerosing cholangitis, n (%)	<5	N.P.	N.P.
Arthropathies, n (%).	<5	N.P.	<5
Psoriasis (ICD10: L40), n (%).	9 (4.5)	75 (2.9)	15 (0.6)
Crohn's Disease (ICD10: K50), n (%).	54 (27.1)	643 (24.4)	400 (17.0)
Number of persons with at least one colonoscopy and/or sigmoidoscopy			
≤1 year before cohort entry, n (%)	139 (69.8)	2,157 (82.0)	1,941 (82.7)
≤2 years before cohort entry, n (%)	156 (78.4)	2,291 (87.1)	2,104 (89.6)
≤3 years before cohort entry, n (%)	171 (85.9)	2,366 (90.0)	2,160 (92.0)
Prior therapy with thiopurine at cohort entry, n (%)	No: 45 (22.6)	No: 1,732 (65.9)	No: N.A.
	Yes: 154 (77.4)	Yes: 898 (34.1)	Yes: N.A.
Prior use of biologic agents (including IFX, ADA, GLM and vedolizumab) at time of cohort entry			
0, n (%)	49 (24.6)	2,352 (89.4)	2,348 (100.0)
1, n (%)	100 (50.3)	265 (10.1)	N.A.
≥2, n (%)	50 (25.1)	13 (0.5)	N.A.
Vedolizumab, n (%)	19 (9.5)	27 (1.0)	N.A.

Abbreviations: ADA: adalimumab; GLM: golimumab; ICD-10: International Classification of Diseases - 10th Revision; IFX: infliximab; N.A.: not applicable; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Patients may enter multiple categories

Table D2B.DK Demographic and clinical characteristics of the patients distributed by therapy cohort[a] entry.

Characteristic	Therapy cohort		
	GLM (N = 595)	**Other Anti-TNF (N = 3,676)**	**TP (N = 2,348)**
Age at cohort entry (in years)			
Mean (SD)	41.1 (16.0)	39.6 (17.0)	41.4 (18.8)
Median (Q1, Q3)	40.2 (28.0, 53.0)	37.2 (25.4, 52.5)	39.6 (25.8, 56.3)
Min, Max	N.P.	N.P.	N.P.
Age group in years, n (%)			
<35	230 (38.7)	1,694 (46.1)	1,011 (43.1)
≥35	365 (61.3)	1,982 (53.9)	1,337 (56.9)
Sex, n (%)			
Male	286 (48.1)	1,837 (50.0)	1,201 (51.1)
Female	309 (51.9)	1,839 (50.0)	1,147 (48.9)
Calendar year of cohort entry, n (%)			
2013	<5	N.P.	N.P.
2014	N.P.	N.P.	N.P.
2015	58 (9.7)	480 (13.1)	375 (16.0)
2016	76 (12.8)	498 (13.5)	354 (15.1)
2017	110 (18.5)	568 (15.5)	327 (13.9)
2018	104 (17.5)	513 (14.0)	319 (13.6)
2019	106 (17.8)	583 (15.9)	281 (12.0)
2020	63 (10.6)	447 (12.2)	188 (8.0)
UC duration (time since first registration of primary UC) in years			
<1	54 (9.1)	1,207 (32.8)	970 (41.3)
1-4	224 (37.6)	1,042 (28.3)	705 (30.0)
5-9	133 (22.4)	584 (15.9)	275 (11.7)
≥10	184 (30.9)	843 (22.9)	398 (17.0)
Maximum extent of disease before or same date as cohort entry, n (%)			

Characteristic	Therapy cohort		
	GLM (N = 595)	**Other Anti-TNF (N = 3,676)**	**TP (N = 2,348)**
E1: Ulcerative proctitis	29 (4.9)	174 (4.7)	120 (5.1)
E2: Left sided UC (distal UC)	66 (11.1)	312 (8.5)	312 (13.3)
E3: Extensive UC (pancolitis)	456 (76.6)	2,626 (71.4)	1,502 (64.0)
Unclassifiable extent	44 (7.4)	564 (15.3)	414 (17.6)
Received at least 2 UC primary diagnoses on or before date of cohort entry, n (%)	No: 42 (7.1)	No: 585 (15.9)	No: 500 (21.3)
	Yes: 553 (92.9)	Yes: 3,091 (84.1)	Yes: 1,848 (78.7)
At least 2 therapies with systemic steroid, ≤1 year before cohort entry, n (%)	No: 334 (56.1)	No: 1,675 (45.6)	No: 844 (35.9)
	Yes: 261 (43.9)	Yes: 2,001 (54.4)	Yes: 1,504 (64.1)
Prior therapy with ciclosporine, ≤1 year before cohort entry, n (%)	No: 595 (100.0)	No: N.P.	No: N.P.
	Yes: 0 (0.0)	Yes: N.P.	Yes: <5
Prior diagnosis (primary or secondary diagnosis) before cohort entry with			
Sclerosing cholangitis, n (%)	9 (1.5)	50 (1.4)	33 (1.4)
Arthropathies, n (%).	N.P.	N.P.	<5
Psoriasis (ICD10: L40), n (%).	16 (2.7)	89 (2.4)	15 (0.6)
Crohn's Disease (ICD10: K50), n (%).	115 (19.3)	877 (23.9)	400 (17.0)
Number of persons with at least one colonoscopy and/or sigmoidoscopy			
≤1 year before cohort entry, n (%)	435 (73.1)	3,040 (82.7)	1,941 (82.7)
≤2 years before cohort entry, n (%)	518 (87.1)	3,264 (88.8)	2,104 (89.6)
≤3 years before cohort entry, n (%)	549 (92.3)	3,366 (91.6)	2,160 (92.0)
Prior therapy with thiopurine at cohort entry, n (%)	No: 127 (21.3)	No: 1,744 (47.4)	No: N.A.
	Yes: 468 (78.7)	Yes: 1,932 (52.6)	Yes: N.A.
Prior use of biologic agents (including IFX, ADA, GLM and vedolizumab) at time of cohort entry			
0, n (%)	64 (10.8)	3,351 (91.2)	2,348 (100.0)
1, n (%)	378 (63.5)	293 (8.0)	N.A.
≥2, n (%)	153 (25.7)	32 (0.9)	N.A.
Vedolizumab, n (%)	64 (10.8)	40 (1.1)	N.A.

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

Abbreviations: ADA: adalimumab; GLM: golimumab; ICD-10: International Classification of Diseases - 10th Revision; IFX: infliximab; N.A.: not applicable; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Patients may enter more than one therapy cohort after therapy switch (i.e. therapy cohort entries are not mutually exclusive)

[b] Patients may enter multiple categories

Table D3.DK The population of unique study persons distributed by initial therapy cohort and subsequent first therapy switch during follow-up.

Initial therapy cohort[a]	Total N[a] (%)	Number of patients switching to the next cohort during follow-up [b]		
		No switch N (%)	GLM N (%)	Other Anti-TNF N (%)
GLM	199 (3.8)	165 (82.9)	N.A.	34 (17.1)
Other Anti-TNF	2,630 (50.8)	2,366 (90.0)	264 (10.0)	N.A.
TP	2,348 (45.4)	1,325 (56.4)	17 (0.7)	1,006 (42.8)

Abbreviations: GLM: golimumab; N.A.: not applicable; TNF: tumor necrosis factor alpha; TP: thiopurine
[a] Number of unique patients by *initial* therapy cohort
[b] Represent the *first switch* after initial therapy cohort entry during study follow-up. Note that switch to TP after being treated with GLM or Other Anti-TNF agents is not relevant for the study

Table D4.DK The population of unique study persons characterized at the initial therapy cohort entry according to status on subsequent switches.

Initial therapy cohort[a] *Selected covariates[b]*	**At least one switch registered[c]**	**No switch registered[c]**
GLM cohort (N = 199)	**N = 34**	**N = 165**
Age in years		
○ Mean (SD)	43.1 (14.6)	44.9 (14.9)
○ Median (Q1, Q3)	41.4 (32.5, 53.0)	43.1 (34.4, 56.4)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	12 (35.3)	44 (26.7)
○ ≥35, n (%)	22 (64.7)	121 (73.3)
Sex, n (%)		
○ Male	11 (32.4)	81 (49.1)
○ Female	23 (67.6)	84 (50.9)
UC duration since first registration of UC until initial study entry in years		
○ <1, n (%)	<5	N.P.
○ 1-4, n (%)	N.P.	N.P.
○ 5-9, n (%)	9 (26.5)	48 (29.1)
○ ≥10, n (%)	15 (44.1)	83 (50.3)
Maximum extent of disease before or same date as cohort entry, n (%)		
○ E1: Ulcerative proctitis	<5	N.P.
○ E2: Left sided UC (distal UC)	<5	N.P.
○ E3: Extensive UC (pancolitis)	27 (79.4)	136 (82.4)
○ Unclassifiable extent	<5	N.P.
○ ≥2 registrations of systemic steroid use in prior 12 months of therapy cohort entry	No: 21 (61.8)	No: 92 (55.8)
	Yes: 13 (38.2)	Yes: 73 (44.2)
○ Prior diagnosis (primary or secondary diagnosis) before cohort entry with Crohn's Disease *(ICD10: K50)*, n (%).	9 (26.5)	45 (27.3)
Prior use of biologic agents (including IFX, ADA, GLM and vedolizumab) at time of cohort entry		
○ 0, n (%)	17 (50.0)	32 (19.4)
○ 1, n (%)	N.P.	N.P.
○ ≥2, n (%)	<5	N.P.
○ Vedolizumab, n (%)	N.P.	N.P.
	<5	N.P.
Other Anti-TNF cohort (N = 2,630)	**N = 264**	**N = 2,366**
Age in years		
○ Mean (SD)	38.2 (16.0)	39.8 (16.9)
○ Median (Q1, Q3)	36.3 (24.9, 50.1)	37.5 (25.5, 52.1)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	124 (47.0)	1,070 (45.2)
○ ≥35, n (%)	140 (53.0)	1,296 (54.8)
Sex, n (%)		
○ Male	134 (50.8)	1,184 (50.0)
○ Female	130 (49.2)	1,182 (50.0)

Initial therapy cohort[a] *Selected covariates*[b]	**At least one switch registered**[c]	**No switch registered**[c]
UC duration since first registration of UC until initial study entry in years		
○ <1, n (%)	94 (35.6)	843 (35.6)
○ 1-4, n (%)	67 (25.4)	531 (22.4)
○ 5-9, n (%)	40 (15.2)	373 (15.8)
○ ≥10, n (%)	63 (23.9)	619 (26.2)
Maximum extent of disease before or same date as cohort entry, n (%)		
○ E1: Ulcerative proctitis	15 (5.7)	112 (4.7)
○ E2: Left sided UC (distal UC)	29 (11.0)	155 (6.6)
○ E3: Extensive UC (pancolitis)	198 (75.0)	1,705 (72.1)
○ Unclassifiable extent	22 (8.3)	394 (16.7)
○ ≥2 registrations of systemic steroid use in prior 12 months of therapy cohort entry	No: 138 (52.3)	No: 1,202 (50.8)
	Yes: 126 (47.7)	Yes: 1,164 (49.2)
○ Prior diagnosis (primary or secondary diagnosis) before cohort entry with Crohn's Disease *(ICD10: K50)*, n (%).	45 (17.0)	598 (25.3)
Prior use of biologic agents (including IFX, ADA, GLM and vedolizumab) at time of cohort entry		
○ 0, n (%)	233 (88.3)	2,119 (89.6)
○ 1, n (%)	N.P.	N.P.
○ ≥2, n (%)	<5	N.P.
○ Vedolizumab, n (%)	N.P.	N.P.
	<5	N.P.
TP cohort (N = 2,348)	**N = 1,023**	**N = 1,325**
Age in years		
○ Mean (SD)	38.3 (17.6)	43.8 (19.2)
○ Median (Q1, Q3)	35.2 (24.0, 52.8)	42.5 (27.6, 59.9)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	507 (49.6)	504 (38.0)
○ ≥35, n (%)	516 (50.4)	821 (62.0)
Sex, n (%)		
○ Male	513 (50.1)	688 (51.9)
○ Female	510 (49.9)	637 (48.1)
UC duration since first registration of UC until initial study entry in years		
○ <1, n (%)	488 (47.7)	482 (36.4)
○ 1-4, n (%)	296 (28.9)	409 (30.9)
○ 5-9, n (%)	112 (10.9)	163 (12.3)
○ ≥10, n (%)	127 (12.4)	271 (20.5)
Maximum extent of disease before or same date as cohort entry, n (%)		
○ E1: Ulcerative proctitis	46 (4.5)	74 (5.6)
○ E2: Left sided UC (distal UC)	126 (12.3)	186 (14.0)
○ E3: Extensive UC (pancolitis)	703 (68.7)	799 (60.3)
○ Unclassifiable extent	148 (14.5)	266 (20.1)
○ ≥2 registrations of systemic steroid use in prior 12 months of therapy cohort entry	No: 321 (31.4)	No: 523 (39.5)
	Yes: 702 (68.6)	Yes: 802 (60.5)

Initial therapy cohort[a] *Selected covariates*[b]	**At least one switch registered**[c]	**No switch registered**[c]
○ Prior diagnosis (primary or secondary diagnosis) before cohort entry with Crohn's Disease *(ICD10: K50)*, n (%).	173 (16.9)	227 (17.1)
Prior use of biologic agents (including IFX, ADA, GLM and vedolizumab) at time of cohort entry		
○ 0, n (%)	1,023 (100.0)	1,325 (100.0)
○ 1, n (%)	N.A.	N.A.
○ ≥2, n (%)	N.A.	N.A.
○ Vedolizumab, n (%)	N.A.	N.A.
	N.A.	N.A.

Abbreviations: ADA: adalimumab; GLM: golimumab; ICD-10: International Classification of Diseases - 10th Revision; IFX: infliximab; N.A.: not applicable; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] The initial therapy cohort to which a study person is entered

[b] Selected covariates judged to be of prior interest (see Text Table 7 and Table D2 for the full list of covariates). Valuated at time of initial therapy cohort entry

[c] Switches internally (between ADA and IFX) in the Other Anti-TNF cohort are ignored

Table D5.DK Description of selected covariates at time of outcomes by therapy cohort[a].

Therapy cohort[a] *Selected covariate[b]*	**Outcome**	
	CRC **N = 30**	**All-cause TC** **N = 897**
GLM cohort	**n < 5**	**n = 115**
Age in years (at outcome)		
○ Mean (SD)	N.P.	42.2 (17.3)
○ Median (Q1, Q3)	N.P.	40.4 (27.2, 55.4)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	N.P.	44 (38.3)
○ ≥35, n (%)	N.P.	71 (61.7)
UC duration (from first UC registration until date of outcome) in years		
○ <1, n (%)	N.P.	8 (7.0)
○ 1-4, n (%)	N.P.	55 (47.8)
○ 5-9, n (%)	N.P.	21 (18.3)
○ ≥10, n (%)	N.P.	31 (27.0)
Other Anti-TNF cohort	**n = 16**	**n = 592**
Age in years (at outcome)		
○ Mean (SD)	49.2 (16.0)	40.2 (17.7)
○ Median (Q1, Q3)	48.4 (34.4, 57.5)	36.3 (24.9, 54.2)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	<5	287 (48.5)
○ ≥35, n (%)	N.P.	305 (51.5)
UC duration (from first UC registration until date of outcome) in years		
○ <1, n (%)	<5	171 (28.9)
○ 1-4, n (%)	<5	215 (36.3)
○ 5-9, n (%)	<5	94 (15.9)
○ ≥10, n (%)	10 (62.5)	112 (18.9)
TP cohort	**n = N.P.**	**N = 190**
Age in years (at outcome)		
○ Mean (SD)	N.P.	42.5 (20.1)
○ Median (Q1, Q3)	N.P.	38.9 (24.9, 60.4)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	N.P.	88 (46.3)
○ ≥35, n (%)	N.P.	102 (53.7)
UC duration (from first UC registration until date of outcome) in years		
○ <1, n (%)	N.P.	38 (20.0)
○ 1-4, n (%)	N.P.	93 (48.9)
○ 5-9, n (%)	N.P.	29 (15.3)
○ ≥10, n (%)	N.P.	30 (15.8)

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients
[b] Selected covariates of prior interest per protocol (see Text Table 7 and Table D2 for the full list of covariates). Time-dependent covariates will be updated continuously

Table D6A.DK Unadjusted incidence rates of study outcomes by therapy cohorts[a]. Unstratified for history of therapy with biologics at cohort entry.

Outcome	Therapy cohort[a]		
	GLM N = 595	**Other Anti-TNF N = 3,676**	**TP N = 2,348**
All-cause TC			
n[b]	115	592	190
Person-years, PY[c]	2,001.4	13,385.3	10,288.4
Crude Incidence rate per 1,000 PY	57.5	44.2	18.5
95% Confidence Interval	47.9, 69.0	40.8, 47.9	16.0, 21.3
CRC (colorectal cancer)			
n[b]	<5	16	N.P.
Person-years, PY[c]	N.P.	15,490.9	N.P.
Crude Incidence rate per 1,000 PY	N.P.	1.0	N.P.
95% Confidence Interval	N.P.	0.6, 1.7	N.P.

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.P.: not permissible; PY: person-years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients

[b] Number of patients with first outcome

[c] For this analysis person-time is from first entry to therapy cohort entry until end of observation

Table D6B.DK Unadjusted incidence rates of study outcomes by therapy cohorts[a]. Stratification: No prior biologics at cohort entry.

Outcome	Therapy cohort[a]		
	GLM N = 64	**Other Anti-TNF N = 3,351**	**TP N = 2,348**
All-cause TC			
n[b]	7	549	190
Person-years, PY[c]	301.7	11,973.1	10,288.4
Crude Incidence rate per 1,000 PY	23.2	45.9	18.5
95% Confidence Interval	11.1, 48.7	42.2, 49.9	16.0, 21.3
CRC (colorectal cancer)			
n[b]	<5	N.P.	N.P.
Person-years, PY[c]	N.P.	N.P.	N.P.
Crude Incidence rate per 1,000 PY	N.P.	N.P.	N.P.
95% Confidence Interval	N.P.	N.P.	N.P.

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.P.: not permissible; PY: person-years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients

[b] Number of patients with first outcome

[c] For this analysis person-time is from first entry to therapy cohort entry until end of observation

Table D6C.DK Unadjusted incidence rates of study outcomes by therapy cohorts[a]. Stratification: History of therapy with one biologic at cohort entry.

Outcome	Therapy cohort[a]		
	GLM N = 378	**Other Anti-TNF N = 293**	**TP N.A.**
All-cause TC			
n[b]	78	N.P	N.A.
Person-years, PY[c]	1,245.9	N.P.	N.A.
Crude Incidence rate per 1,000 PY	62.6	N.P.	N.A.
95% Confidence Interval	50.1, 78.2	N.P.	N.A.
CRC (colorectal cancer)			
n[b]	<5	N.P.	N.A.
Person-years, PY[c]	N.P.	N.P.	N.A.
Crude Incidence rate per 1,000 PY	N.P.	N.P.	N.A.
95% Confidence Interval	N.P.	N.P.	N.A.

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.A.: not applicable; N.P.: not permissible; PY: person-years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients

[b] Number of patients with first outcome

[c] For this analysis person-time is from first entry to therapy cohort entry until end of observation

Table D6D.DK Unadjusted incidence rates of study outcomes by therapy cohorts[a]. Stratification: History of therapy with two or more biologics at cohort entry.

Outcome	Therapy cohort[a]		
	GLM N = 153	**Other Anti-TNF N = 32**	**TP N.A.**
All-cause TC			
n[b]	30	<5	N.A.
Person-years, PY[c]	453.8	N.P.	N.A.
Crude Incidence rate per 1,000 PY	66.1	N.P.	N.A.
95% Confidence Interval	46.2, 94.6	N.P.	N.A.
CRC (colorectal cancer)			
n[b]	<5	N.P.	N.A.
Person-years, PY[c]	N.P.	N.P.	N.A.
Crude Incidence rate per 1,000 PY	N.P.	N.P.	N.A.
95% Confidence Interval	N.P.	N.P.	N.A.

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.A.: not applicable; PY: person-years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients

[b] Number of patients with first outcome

[c] For this analysis person-time is from first entry to therapy cohort entry until end of observation

Figure D3.DK Cumulative incidence (with 95% C.I.) of CRC in the population of unique study persons since entry to initial therapy cohort.

Note: The corresponding Kaplan-Meier plot cannot be shown, as otherwise stated in the SAP due to the Danish implementation of the GDPR.

Number of patients included:	5,177
Number of CRC cases:	27
Person-years, total:	23,137.4
Person-years, mean:	4.5
Person-years, min, max):	N.P.
Rate per 1,000 (with 95% CI)	1.2 (0.8, 1.7)

Abbreviations: CI: confidence interval; CRC: colorectal cancer; GDPR: General data protection regulation; N.P.: not permissible; SAP: Statistical Analysis Plan

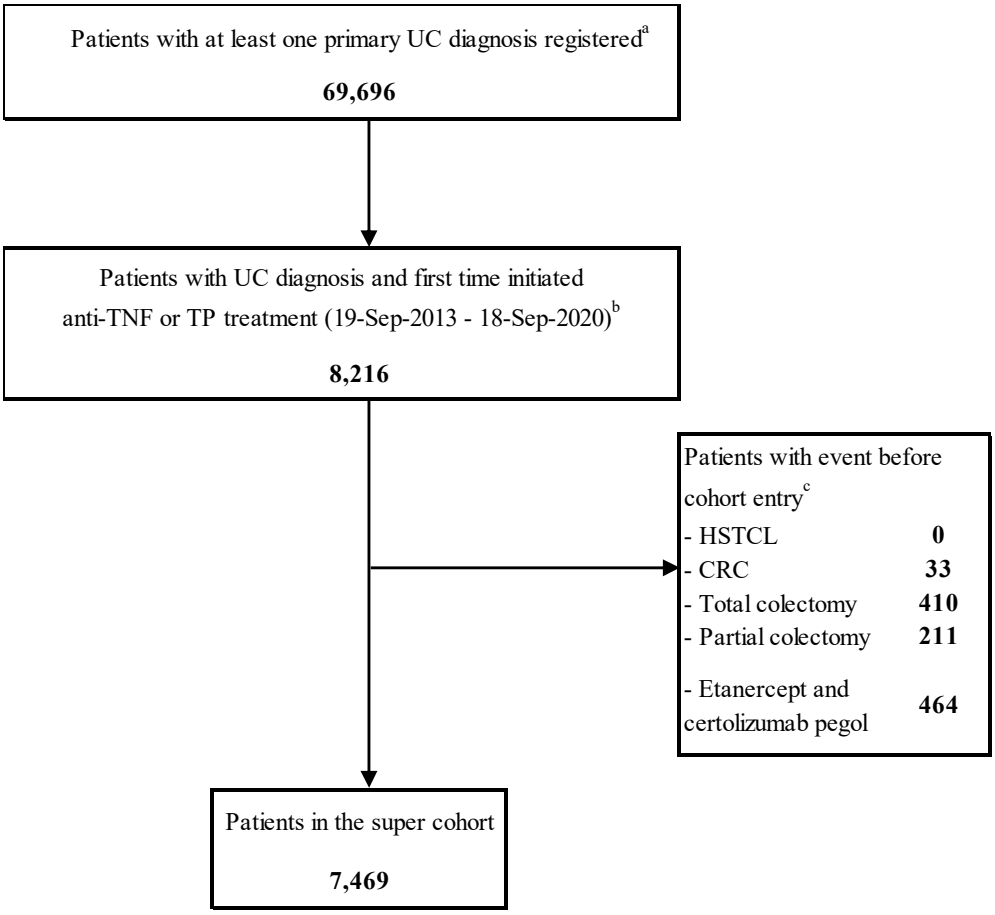
Figure D4.DK Cumulative incidence of first occurrence of all-cause TC in the population of unique study persons since entry to initial therapy cohort.

Note: The corresponding Kaplan-Meier plot cannot be shown, as otherwise stated in the SAP due to the Danish implementation of the GDPR.

Number of patients included:	5,177
Number of total colectomies:	686
Person-years, total:	20,751.6
Person-years, mean:	4,0
Person-years, min, max):	N.P.
Rate per 1,000 (with 95% CI)	33.1 (30.6, 35.6)

Abbreviations: CI: confidence interval; GDPR: General data protection regulation; N.P.: not permissible; SAP: Statistical Analysis Plan; TC: total colectomy;

Figure D1.SE Summary flow diagram of the establishment of population of unique patients (the super cohort).



Abbreviations: CRC: colorectal cancer; HSTCL: hepatosplenic T-cell lymphoma; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis

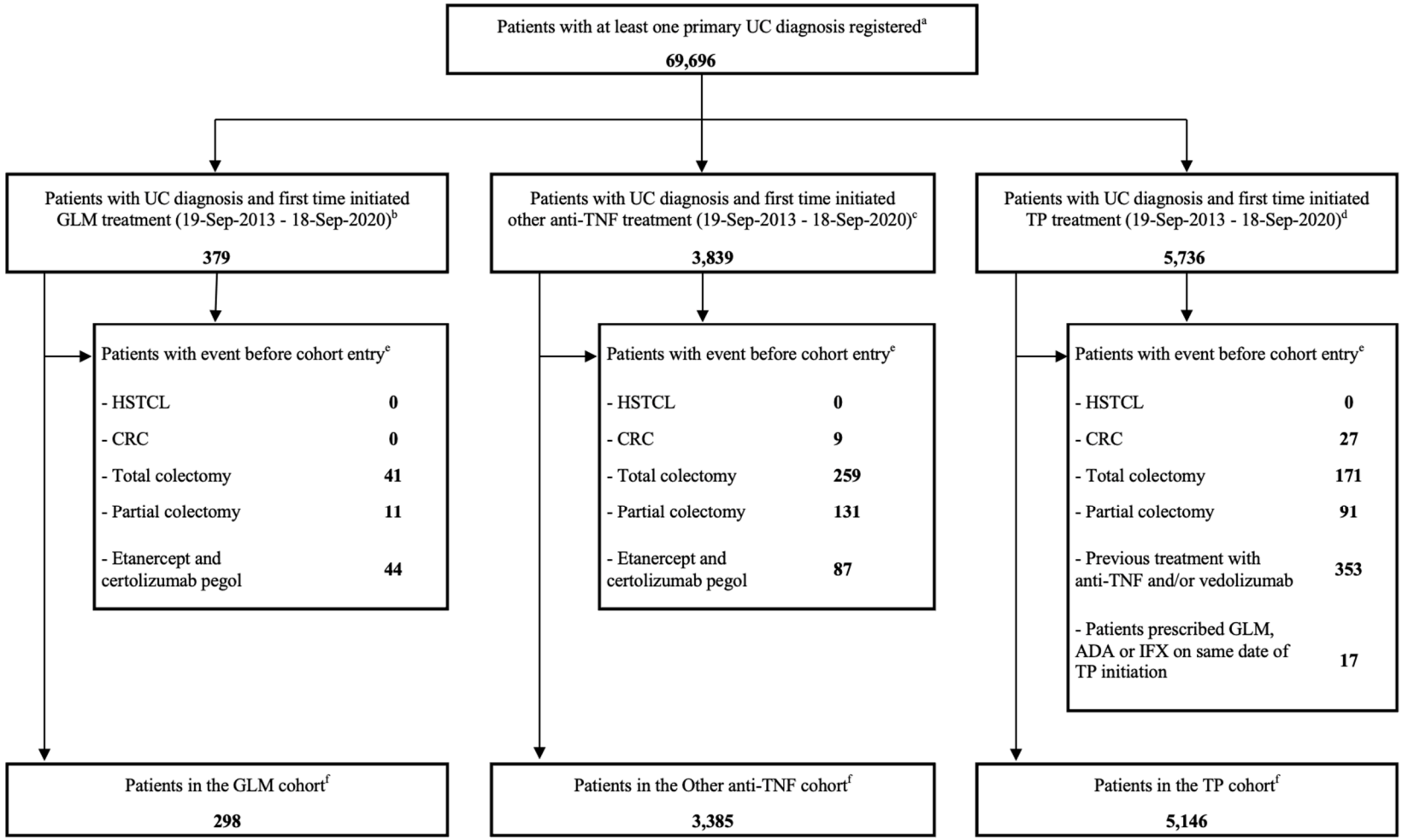
[a] Ascertainment is based on both inpatients and outpatient contacts registered in the National Patient Register until newest available data. Inclusion date of patients refers to "admission date" for inpatient for hospitalized patients and "date of first visit" for outpatient contacts

[b] UC must have been registered as the primary discharge diagnosis before or, at latest, at the event that qualifies for therapy cohort entry

The assignment to super cohort is determined by the first qualifying therapy occasion after 19 September 2013.

[c] A patient can have more than one of the exclusion criteria. The sum of exclusions can therefore exceed the number of patients excluded. Patients entering the cohort of TP therapy must be naïve to any anti-TNF and/or vedolizumab

Figure D2.SE Summary flow diagram of the establishment of therapy cohorts.



Abbreviations: CRC: colorectal cancer; GLM: golimumab; HSTCL: hepatosplenic T-cell lymphoma; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis

[a] Ascertainment is based on both inpatient and outpatient contacts registered in the National Patient Register until newest available data. Inclusion date of patients refers to "admission date" for hospitalized patients and "date of first visit" for outpatient contacts
UC must have been registered as the primary discharge diagnosis before or, at latest, at the event that qualifies for therapy cohort entry
For all three therapy cohorts, the assignment to therapy cohort is determined by the first qualifying therapy occasion after 19 September 2013.

[b] The therapy cohort of UC patients treated with GLM (the GLM cohort) is defined as all patients who for the first time are registered with GLM from 19 September 2013. The patients in the GLM cohort can be former users of the Other Anti-TNF agents as well as TP. Last date of cohort entry: 18 September 2020

[c] The therapy cohort of UC patients treated with IFX or ADA (Other Anti-TNF cohort) is defined as all patients who for the first time are registered with IFX or ADA from 19 September 2013. Hence, ADA users must be naïve to ADA and IFX users must be naïve to IFX but ADA users may have used IFX before, and IFX may have used ADA before. The patients in the Other Anti-TNF cohort can be former users of GLM as well as TP. Last date of cohort entry: 18 September 2020

[d] The therapy cohort of TP patients (the TP cohort) is defined as all patients who for the first time are registered with TP (ATC: *L01BB02* or *L04AX01*) from 19 September 2013. Users must be naïve to both TP, anti-TNF therapy and vedolizumab (ATC *L04AA33*). Last date of cohort entry: 18 September 2020

[e] A patient can have more than one of the exclusion criteria. The sum of exclusions can therefore exceed the number of patients excluded

[f] A patient can enter more than one cohort if qualification criteria for entering another cohort are met after entering a specific cohort. The flow chart accounts for all cohort entries which totals to more than the number of unique patients represented in all therapy cohorts grouped together

Table D1.SE Number of entries and duration of follow-up[a], by therapy cohorts and year of first-time entry to the therapy cohort.

Measures	Therapy cohort		
	GLM (N = 298)	**Other Anti-TNF (N = 3,385)**	**TP (N = 5,146)**
All study entry years, n	298	3,385	5,146
Person-years of follow-up[a]	1,285.7	11,247.4	19,803.5
Mean (SD)	4.3 (1.9)	3.3 (2.1)	3.8 (2.0)
Median (Q1, Q3)	4.5 (2.7, 6.0)	3.0 (1.5, 5.2)	3.9 (2.1, 5.6)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2013, n	6	120	238
Person-years of follow-up[a]	42.9	852.0	1,674.1
Mean (SD)	N.P.	7.1 (0.2)	7.0 (0.7)
Median (Q1, Q3)	N.P.	7.1 (7.1, 7.2)	7.1 (7.1, 7.2)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2014, n	72	414	780
Person-years of follow-up[a]	459.8	2,639.7	4,994.9
Mean (SD)	6.4 (0.5)	6.4 (0.8)	6.4 (0.7)
Median (Q1, Q3)	6.4 (6.2, 6.7)	6.5 (6.2, 6.8)	6.5 (6.2, 6.8)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2015, n	60	432	740
Person-years of follow-up[a]	324.5	2,363.9	3,975.6
Mean (SD)	5.4 (0.5)	5.5 (0.5)	5.4 (0.7)
Median (Q1, Q3)	5.5 (5.2, 5.7)	5.5 (5.2, 5.8)	5.5 (5.2, 5.7)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2016, n	36	373	784
Person-years of follow-up[a]	160.3	1,655.4	3,461.9
Mean (SD)	4.5 (0.3)	4.4 (0.5)	4.4 (0.6)
Median (Q1, Q3)	4.5 (4.2, 4.8)	4.5 (4.2, 4.7)	4.5 (4.2, 4.7)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2017, n	41	367	759
Person-years of follow-up[a]	142.0	1,256.3	2,628.7
Mean (SD)	3.5 (0.4)	3.4 (0.5)	3.5 (0.4)
Median (Q1, Q3)	3.5 (3.2, 3.8)	3.4 (3.2, 3.7)	3.5 (3.2, 3.8)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2018, n	41	425	677
Person-years of follow-up[a]	103.5	1,038.3	1,670.9
Mean (SD)	2.5 (0.3)	2.4 (0.3)	2.5 (0.4)
Median (Q1, Q3)	2.6 (2.3, 2.7)	2.5 (2.2, 2.7)	2.5 (2.2, 2.8)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2019, n	31	743	752
Person-years of follow-up[a]	45.8	1,118.0	1,124.2
Mean (SD)	1.5 (0.3)	1.5 (0.3)	1.5 (0.3)
Median (Q1, Q3)	1.4 (1.2, 1.7)	1.5 (1.3, 1.7)	1.5 (1.2, 1.8)
Min, Max	N.P.	N.P.	N.P.
Cohort entry 2020, n[b]	11	511	416
Person-years of follow-up[a]	6.9	323.8	273.1
Mean (SD)	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)

Measures	Therapy cohort		
	GLM (N = 298)	**Other Anti-TNF (N = 3,385)**	**TP (N = 5,146)**
Median (Q1, Q3)	N.P.	0.6 (0.5, 0.8)	0.7 (0.5, 0.9)
Min, Max	N.P.	N.P.	N.P.

Abbreviations: GLM: golimumab; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Note: For this table, duration of follow-up is based on the date of entry to a therapy cohort until the first event of death, emigration or end of data-collection (31 October 2021). therapy cohort entries are not mutually exclusive. Thus, patients entering more than one therapy cohort will contribute follow-up time to each cohort

[b] Latest possible date of recruitment of new study persons is 18 September 2020, but switches to other therapy cohorts may take place until end of data collection (31 December 2020)

Table D2A.SE Demographic and clinical characteristics of unique patients distributed by initial therapy cohorts

Characteristic	Initial therapy cohort		
	GLM (N = 151)	**Other Anti-TNF (N = 2,172)**	**TP (N = 5,146)**
Age at cohort entry (in years)			
Mean (SD)	42.9 (14.6)	39.4 (15.9)	38.1 (18.5)
Median (Q1, Q3)	41.0 (31.1, 54.7)	37.4 (26.3, 50.5)	33.7 (23.4, 52.5)
Min, Max	N.P.	N.P.	N.P.
Age group in years, n (%)			
<35	51 (33.8)	980 (45.1)	2,695 (52.4)
≥35	100 (66.2)	1,192 (54.9)	2,451 (47.6)
Sex, n (%)			
Male	63 (41.7)	1,153 (53.1)	2,904 (56.4)
Female	88 (58.3)	1,019 (46.9)	2,242 (43.6)
Calendar year of cohort entry, n (%)			
2013	6 (4.0)	117 (5.4)	238 (4.6)
2014	58 (38.4)	333 (15.3)	780 (15.2)
2015	28 (18.5)	287 (13.2)	740 (14.4)
2016	N.P.	N.P.	784 (15.2)
2017	20 (13.2)	212 (9.8)	759 (14.7)
2018	15 (9.9)	260 (12.0)	677 (13.2)
2019	7 (4.6)	431 (19.8)	752 (14.6)
2020	<5	N.P.	416 (8.1)
UC duration (time since first registration of primary UC) in years, n (%)			
<1	5 (3.3)	424 (19.5)	2,204 (42.8)
1-4	39 (25.8)	469 (21.6)	1,461 (28.4)
5-9	36 (23.8)	495 (22.8)	607 (11.8)
≥10	71 (47.0)	784 (36.1)	874 (17.0)
Maximum extent of disease before or same date as cohort entry, n (%)			
E1: Ulcerative proctitis	11 (7.3)	119 (5.5)	295 (5.7)

Characteristic	Initial therapy cohort		
	GLM (N = 151)	**Other Anti-TNF (N = 2,172)**	**TP (N = 5,146)**
E2: Left sided UC (distal UC)	18 (11.9)	390 (18.0)	1,188 (23.1)
E3: Extensive UC (pancolitis)	99 (65.6)	1,291 (59.4)	2,825 (54.9)
Unclassifiable extent	23 (15.2)	372 (17.1)	838 (16.3)
Received at least 2 UC primary diagnoses on or before date of cohort entry, n (%)	No: 12 (7.9)	No: 305 (14.0)	No: 679 (13.2)
	Yes: 139 (92.1)	Yes: 1,867 (86.0)	Yes: 4,467 (86.8)
At least 2 therapy courses with systemic steroid, ≤1 year before cohort entry, n (%)	No: 80 (53.0)	No: 1,081 (49.8)	No: 1,881 (36.6)
	Yes: 71 (47.0)	Yes: 1,091 (50.2)	Yes: 3,265 (63.4)
Prior therapy with ciclosporine, ≤1 year before cohort entry, n (%)	No: N.P.	No: 2,165 (99.7)	No: N.P.
	Yes: N.P.	Yes: 7 (0.3)	Yes: <5
Prior diagnosis (primary or secondary diagnosis)[a] before cohort entry with			
Sclerosing cholangitis, n (%)	6 (4.0)	78 (3.6)	141 (2.7)
Arthropathies, n (%).	30 (19.9)	222 (10.2)	73 (1.4)
Psoriasis (ICD10: L40), n (%).	<5	36 (1.7)	25 (0.5)
Crohn's Disease (ICD10: K50), n (%).	51 (33.8)	766 (35.3)	904 (17.6)
Number of persons with at least one colonoscopy and/or sigmoidoscopy			
≤1 year before cohort entry, n (%)	85 (56.3)	1,406 (64.7)	3,733 (72.5)
≤2 years before cohort entry, n (%)	105 (69.5)	1,644 (75.7)	4,203 (81.7)
≤3 years before cohort entry, n (%)	113 (74.8)	1,749 (80.5)	4,399 (85.5)
Prior therapy with thiopurine at cohort entry, n (%)	No: 51 (33.8)	No: 986 (45.4)	N.A.
	Yes: 100 (66.2)	Yes: 1,186 (54.6)	N.A.
Prior use of biologic agents (including IFX, ADA, GLM and VEDO) at time of cohort entry			
0, n (%)	93 (61.6)	N.P.	5,146 (100.0)
1, n (%)	50 (33.1)	153 (7.0)	N.A.
≥2, n (%)	8 (5.3)	<5	N.A.
Vedolizumab, n (%)	0 (0.0)	9 (0.4)	N.A.

Abbreviations: ADA: adalimumab; GLM: golimumab; ICD-10: International Classification of Diseases - 10th Revision; IFX: infliximab; N.A.: not applicable; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Patients may enter multiple categories

Table D2B.SE Demographic and clinical characteristics of the patients distributed by therapy cohort[a] entry.

Characteristic	Therapy cohort		
	GLM (N = 298)	**Other Anti-TNF (N = 3,385)**	**TP (N = 5,146)**
Age at cohort entry (in years)			
Mean (SD)	41.4 (14.9)	38.3 (16.2)	38.1 (18.5)
Median (Q1, Q3)	38.7 (29.3, 50.9)	35.8 (25.5, 49.7)	33.7 (23.4, 52.5)
Min, Max	N.P.	N.P.	N.P.
Age group in years, n (%)			
<35	114 (38.3)	1,644 (48.6)	2,695 (52.4)
≥35	184 (61.7)	1,741 (51.4)	2,451 (47.6)
Sex, n (%)			
Male	141 (47.3)	1,804 (53.3)	2,904 (56.4)
Female	157 (52.7)	1,581 (46.7)	2,242 (43.6)
Calendar year of cohort entry, n (%)			
2013	6 (2.0)	120 (3.5)	238 (4.6)
2014	72 (24.2)	414 (12.2)	780 (15.2)
2015	60 (20.1)	432 (12.8)	740 (14.4)
2016	36 (12.1)	373 (11.0)	784 (15.2)
2017	41 (13.8)	367 (10.8)	759 (14.7)
2018	41 (13.8)	425 (12.6)	677 (13.2)
2019	31 (10.4)	743 (21.9)	752 (14.6)
2020	11 (3.7)	511 (15.1)	416 (8.1)
UC duration (time since first registration of primary UC) in years, n (%)			
<1	18 (6.0)	681 (20.1)	2,204 (42.8)
1-4	94 (31.5)	1,032 (30.5)	1,461 (28.4)
5-9	66 (22.1)	692 (20.4)	607 (11.8)
≥10	120 (40.3)	980 (29.0)	874 (17.0)

Characteristic	Therapy cohort		
	GLM (N = 298)	**Other Anti-TNF (N = 3,385)**	**TP (N = 5,146)**
Maximum extent of disease before or same date as cohort entry, n (%)			
E1: Ulcerative proctitis	18 (6.0)	174 (5.1)	295 (5.7)
E2: Left sided UC (distal UC)	40 (13.4)	635 (18.8)	1,188 (23.1)
E3: Extensive UC (pancolitis)	205 (68.8)	2,015 (59.5)	2,825 (54.9)
Unclassifiable extent	35 (11.7)	561 (16.6)	838 (16.3)
Received at least 2 UC primary diagnoses on or before date of cohort entry, n (%)	No: 17 (5.7)	No: 426 (12.6)	No: 679 (13.2)
	Yes: 281 (94.3)	Yes: 2,959 (87.4)	Yes: 4,467 (86.8)
At least 2 therapy courses with systemic steroid, ≤1 year before cohort entry, n (%)	No: 138 (46.3)	No: 1,505 (44.5)	No: 1,881 (36.6)
	Yes: 160 (53.7)	Yes: 1,880 (55.5)	Yes: 3,265 (63.4)
Prior therapy with ciclosporine, ≤1 year before cohort entry, n (%)	No: N.P.	No: 3,377 (99.8)	No: N.P.
	Yes: <5	Yes: 8 (0.2)	Yes: <5
Prior diagnosis (primary or secondary diagnosis)[b] before cohort entry with			
Sclerosing cholangitis, n (%)	13 (4.4)	118 (3.5)	141 (2.7)
Arthropathies, n (%).	52 (17.4)	260 (7.7)	73 (1.4)
Psoriasis (ICD10: L40), n (%).	7 (2.3)	44 (1.3)	25 (0.5)
Crohn's Disease (ICD10: K50), n (%).	106 (35.6)	1,109 (32.8)	904 (17.6)
Number of persons with at least one colonoscopy and/or sigmoidoscopy			
≤1 year before cohort entry, n (%)	198 (66.4)	2,278 (67.3)	3,733 (72.5)
≤2 years before cohort entry, n (%)	236 (79.2)	2,663 (78.7)	4,203 (81.7)
≤3 years before cohort entry, n (%)	251 (84.2)	2,814 (83.1)	4,399 (85.5)
Prior therapy with thiopurine at cohort entry, n (%)	No: 75 (25.2)	No: 999 (29.5)	N.A.
	Yes: 223 (74.8)	Yes: 2,386 (70.5)	N.A.
Prior use of biologic agents (including IFX, ADA, GLM and VEDO) at time of cohort entry			
0, n (%)	119 (39.9)	3,198 (94.5)	5,146 (100.0)
1, n (%)	142 (47.7)	179 (5.3)	N.A.

Characteristic	Therapy cohort		
	GLM (N = 298)	**Other Anti-TNF (N = 3,385)**	**TP (N = 5,146)**
≥2, n (%)	37 (12.4)	8 (0.2)	N.A.
Vedolizumab, n (%)	6 (2.0)	13 (0.4)	N.A.

Abbreviations: ADA: adalimumab; GLM: golimumab; ICD-10: International Classification of Diseases - 10th Revision; IFX: infliximab; N.A.: not applicable; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Patients may enter more than one therapy cohort after therapy switch (i.e. therapy cohort entries are not mutually exclusive)

[b] Patients may enter multiple categories

Table D3.SE The population of unique study persons distributed by initial therapy cohort and subsequent first therapy switch during follow-up.

Initial therapy cohort[a]	Total N[a] (%)	Number of patients switching to the next cohort during follow-up [b]		
		No switch N (%)	GLM N (%)	Other Anti-TNF N (%)
GLM	151 (2.0)	125 (82.8)	N.A.	26 (17.2)
Other Anti-TNF	2,172 (29.1)	2,081 (95.8)	91 (4.2)	N.A.
TP	5,146 (68.9)	3,934 (76.4)	26 (0.5)	1,186 (23.0)

Abbreviations: GLM: golimumab; N.A.: not applicable; TNF: tumor necrosis factor alpha; TP: thiopurine
[a] Number of unique patients by *initial* therapy cohort
[b] Represent the *first switch* after initial therapy cohort entry during study follow-up. Note that switch to TP after being treated with GLM or Other Anti-TNF agents is not relevant for the study.

Table D4.SE The population of unique study persons characterized at the initial therapy cohort entry according to status on subsequent switches.

Initial therapy cohort[a] *Selected covariates*[b]	**At least one switch registered**[c]	**No switch registered**[c]
GLM cohort (N = 151)	**N = 26**	**N = 125**
Age in years		
○ Mean (SD)	45.5 (16.4)	42.4 (14.2)
○ Median (Q1, Q3)	41.5 (32.9, 56.2)	41.0 (31.1, 53.0)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	8 (30.8)	43 (34.4)
○ ≥35, n (%)	18 (69.2)	82 (65.6)
Sex, n (%)		
○ Male	9 (34.6)	54 (43.2)
○ Female	17 (65.4)	71 (56.8)
UC duration since first registration of UC until initial study entry in years		
○ <1, n (%)	0 (0.0)	5 (4.0)
○ 1-4, n (%)	6 (23.1)	33 (26.4)
○ 5-9, n (%)	5 (19.2)	31 (24.8)
○ ≥10, n (%)	15 (57.7)	56 (44.8)
Maximum extent of disease before or same date as cohort entry, n (%)		
○ E1: Ulcerative proctitis	<5	N.P.
○ E2: Left sided UC (distal UC)	5 (19.2)	13 (10.4)
○ E3: Extensive UC (pancolitis)	17 (65.4)	82 (65.6)
○ Unclassifiable extent	<5	N.P.
○ >2 registrations of systemic steroid use in prior 12 months of therapy cohort entry	No: 12 (46.2)	No: 68 (54.4)
	Yes: 14 (53.8)	Yes: 57 (45.6)
○ Prior diagnosis (primary or secondary diagnosis) before cohort entry with Crohn's Disease (ICD10: K50), n (%).	7 (26.9)	44 (35.2)
Prior use of biologic agents (including IFX, ADA, GLM and VEDO) at time of cohort entry		
○ 0, n (%)	22 (84.6)	71 (56.8)
○ 1, n (%)	<5	N.P.
○ >2, n (%)	N.P.	N.P.
○ Vedolizumab, n (%)	No: 26 (100.0)	No: 125 (100.0)
	Yes: 0 (0.0)	Yes: 0 (0.0)
Other Anti-TNF cohort (N = 2,172)	**N = 91**	**N = 2,081**
Age in years		
○ Mean (SD)	40.0 (14.8)	39.4 (15.9)
○ Median (Q1, Q3)	38.1 (27.2, 49.4)	37.4 (26.2, 50.6)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	37 (40.7)	943 (45.3)
○ ≥35, n (%)	54 (59.3)	1,138 (54.7)
Sex, n (%)		

Initial therapy cohort[a] *Selected covariates*[b]	**At least one switch registered**[c]	**No switch registered**[c]
○ Male	46 (50.5)	1,107 (53.2)
○ Female	45 (49.5)	974 (46.8)
UC duration since first registration of UC until initial study entry in years		
○ <1, n (%)	13 (14.3)	411 (19.8)
○ 1-4, n (%)	26 (28.6)	443 (21.3)
○ 5-9, n (%)	24 (26.4)	471 (22.6)
○ ≥10, n (%)	28 (30.8)	756 (36.3)
Maximum extent of disease before or same date as cohort entry, n (%)		
○ E1: Ulcerative proctitis	<5	N.P.
○ E2: Left sided UC (distal UC)	N.P.	N.P.
○ E3: Extensive UC (pancolitis)	69 (75.8)	1,222 (58.7)
○ Unclassifiable extent	8 (8.8)	364 (17.5)
○ >2 registrations of systemic steroid use in prior 12 months of therapy cohort entry	No: 36 (39.6)	No: 1,045 (50.2)
	Yes: 55 (60.4)	Yes: 1,036 (49.8)
○ Prior diagnosis (primary or secondary diagnosis) before cohort entry with Crohn's Disease (ICD10: K50), n (%).	36 (39.6)	730 (35.1)
Prior use of biologic agents (including IFX, ADA, GLM and VEDO) at time of cohort entry		
○ 0, n (%)	81 (89.0)	1,934 (92.9)
○ 1, n (%)	N.P.	N.P.
○ >2, n (%)	N.P.	<5
○ Vedolizumab, n (%)	No: N.P.	No: N.P.
	Yes: <5	Yes: N.P.
TP cohort (N = 5,146)	**N = 1,212**	**N = 3,934**
Age in years		
○ Mean (SD)	34.9 (16.5)	39.1 (19.0)
○ Median (Q1, Q3)	31.4 (22.4, 46.2)	34.7 (24.0, 54.4)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	702 (57.9)	1,993 (50.7)
○ ≥35, n (%)	510 (42.1)	1,941 (49.3)
Sex, n (%)		
○ Male	660 (54.5)	2,244 (57.0)
○ Female	552 (45.5)	1,690 (43.0)
UC duration since first registration of UC until initial study entry in years		
○ <1, n (%)	598 (49.3)	1,606 (40.8)
○ 1-4, n (%)	340 (28.1)	1,121 (28.5)
○ 5-9, n (%)	122 (10.1)	485 (12.3)
○ ≥10, n (%)	152 (12.5)	722 (18.4)
Maximum extent of disease before or same date as cohort entry, n (%)		
○ E1: Ulcerative proctitis	55 (4.5)	240 (6.1)
○ E2: Left sided UC (distal UC)	246 (20.3)	942 (23.9)

Initial therapy cohort[a] *Selected covariates*[b]	**At least one switch registered**[c]	**No switch registered**[c]
○ E3: Extensive UC (pancolitis)	725 (59.8)	2,100 (53.4)
○ Unclassifiable extent	186 (15.3)	652 (16.6)
○ >2 registrations of systemic steroid use in prior 12 months of therapy cohort entry	No: 425 (35.1)	No: 1,456 (37.0)
	Yes: 787 (64.9)	Yes: 2,478 (63.0)
○ Prior diagnosis (primary or secondary diagnosis) before cohort entry with Crohn's Disease (ICD10: K50), n (%).	251 (20.7)	653 (16.6)
Prior use of biologic agents (including IFX, ADA, GLM and vedolizumab) at time of cohort entry		
○ 0, n (%)	1,212 (100.0)	3,934 (100.0)
○ 1, n (%)	N.A.	N.A.
○ >2, n (%)	N.A.	N.A.
○ Vedolizumab, n (%)	No: N.A.	No: N.A.
	Yes: N.A.	Yes: N.A.

Abbreviations: ADA: adalimumab; GLM: golimumab; ICD-10: International Classification of Diseases - 10th Revision; IFX: infliximab; N.A.: not applicable; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] The initial therapy cohort to which a study person is entered

[b] Selected covariates judged to be of prior interest (see Text Table 7 and Table D2 for the full list of covariates). Valuated at time of initial therapy cohort entry

[c] Switches internally (between ADA and IFX) in the Other Anti-TNF cohort are ignored

Table D5.SE Description of selected covariates at time of outcomes by therapy cohort[a].

Therapy cohort[a] *Selected covariate[b]*	**Outcome**	
	CRC **N = 47**	**All-cause TC** **N = 602**
GLM cohort	**n = <5**	**n = 41**
Age in years (at outcome)		
○ Mean (SD)	N.P.	40.7 (14.0)
○ Median (Q1, Q3)	N.P.	39.9 (30.9, 49.3)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	<5	N.P.
○ ≥35, n (%)	<5	N.P.
UC duration (from first UC registration until date of outcome) in years		
○ <1, n (%)	N.P.	<5
○ 1-4, n (%)	0 (0.0)	10 (24.4)
○ 5-9, n (%)	<5	15 (36.6)
○ ≥10, n (%)	<5	N.P.
Other Anti-TNF cohort	**n = N.P.**	**n = 298**
Age in years (at outcome)		
○ Mean (SD)	51.7 (15.5)	39.4 (17.3)
○ Median (Q1, Q3)	53.0 (37.0, 64.3)	33.6 (25.9, 53.0)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	<5	157 (52.7)
○ ≥35, n (%)	N.P.	141 (47.3)
UC duration (from first UC registration until date of outcome) in years		
○ <1, n (%)	N.P.	36 (12.1)
○ 1-4, n (%)	<5	114 (38.3)
○ 5-9, n (%)	5 (23.8)	65 (21.8)
○ ≥10, n (%)	14 (66.7)	83 (27.9)
TP cohort	**n = 22**	**n = 263**
Age in years (at outcome)		
○ Mean (SD)	61.3 (18.9)	41.8 (19.3)
○ Median (Q1, Q3)	66.9 (54.6, 74.6)	37.8 (25.3, 59.7)
○ Min, Max	N.P.	N.P.
○ <35, n (%)	<5	125 (47.5)
○ ≥35, n (%)	N.P.	138 (52.5)
UC duration (from first UC registration until date of outcome) in years		
○ <1, n (%)	0	48 (18.3)
○ 1-4, n (%)	5 (22.7)	134 (51.0)
○ 5-9, n (%)	9 (40.9)	39 (14.8)
○ ≥10, n (%)	8 (36.4)	42 (16.0)

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.P.: not permissible; Q1: first quartile; Q3: third quartile; SD: standard deviation; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients
[b] Selected covariates of prior interest per protocol (see Text Table 7 and Table D2 for the full list of covariates). Time-dependent covariates will be updated continuously

Table D6A.SE Unadjusted incidence rates of study outcomes by therapy cohorts[a]. Unstratified for history of therapy with biologics at cohort entry.

Outcome	Therapy cohort[a]		
	GLM N = 298	**Other Anti-TNF N = 3,385**	**TP N = 5,146**
All-cause TC			
n[b]	41	298	263
Person-years, PY[c]	1,142.0	10,318.4	19,027.1
Crude Incidence rate per 1,000 PY	35.9	28.9	13.8
95% Confidence Interval	26.4, 48.8	25.8, 32.4	12.2, 15.6
CRC (colorectal cancer)			
n[b]	<5	N.P.	22
Person-years, PY[c]	1,281.1	11,211.6	19,757.2
Crude Incidence rate per 1,000 PY	N.P.	N.P.	1.1
95% Confidence Interval	N.P.	N.P.	0.7, 1.7

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.P.: not permissible; PY: person-years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort, outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients

[b] Number of patients with first outcome

[c] For this analysis person-time is from first entry to therapy cohort entry until end of observation

Table D6B.SE Unadjusted incidence rates of study outcomes by therapy cohorts[a]. Stratification: No prior biologics at cohort entry.

Outcome	Therapy cohort[a]		
	GLM N = 119	**Other Anti-TNF N = 3,198**	**TP N = 5,146**
All-cause TC			
n[b]	16	278	263
Person-years, PY[c]	539.6	9,621.1	19,027.1
Crude Incidence rate per 1,000 PY	29.7	28.9	13.8
95% Confidence Interval	18.2, 48.4	25.7, 32.5	12.2, 15.6
CRC (colorectal cancer)			
n[b]	<5	N.P.	22
Person-years, PY[c]	591.0	10,451.4	19,757.2
Crude Incidence rate per 1,000 PY	N.P.	N.P.	1.1
95% Confidence Interval	N.P.	N.P.	0.7, 1.7

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.P.: not permissible; PY: person-years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort, outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients

[b] Number of patients with first outcome

[c] For this analysis person-time is from first entry to therapy cohort entry until end of observation

Table D6C.SE Unadjusted incidence rates of study outcomes by therapy cohorts[a].
Stratification: History of therapy with one biologic at cohort entry.

Outcome	Therapy cohort[a]		
	GLM N = 142	**Other Anti-TNF N = 179**	**TP N.A.**
All-cause TC			
n[b]	19	20	N.A.
Person-years, PY[c]	485.1	675.2	N.A.
Crude Incidence rate per 1,000 PY	39.2	29.6	N.A.
95% Confidence Interval	25.0, 61.4	19.1, 45.9	N.A.
CRC (colorectal cancer)			
n[b]	0	<5	N.A.
Person-years, PY[c]	546.5	738.1	N.A.
Crude Incidence rate per 1,000 PY	0.0	N.P.	N.A.
95% Confidence Interval	N.A.	N.P.	N.A.

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.A.: not applicable; N.P.: not permissible; PY: person-years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients

[b] Number of patients with first outcome

[c] For this analysis person-time is from first entry to therapy cohort entry until end of observation

Table D6D.SE Unadjusted incidence rates of study outcomes by ttherapy cohorts[a].
Stratification: History of therapy with two or more biologics at cohort entry.

Outcome	Therapy cohort[a]		
	GLM N = 37	**Other Anti-TNF N = 8**	**TP N.A.**
All-cause TC			
n[b]	6	0	N.A.
Person-years, PY[c]	117.3	22.1	N.A.
Crude Incidence rate per 1,000 PY	51.1	0.0	N.A.
95% Confidence Interval	23.0, 113.8	N.A.	N.A.
CRC (colorectal cancer)			
n[b]	0	0	N.A.
Person-years, PY[c]	143.6	22.1	N.A.
Crude Incidence rate per 1,000 PY	0.0	0.0	N.A.
95% Confidence Interval	N.A.	N.A.	N.A.

Abbreviations: CRC: colorectal cancer; GLM: golimumab; N.A.: not applicable; PY: person-years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients

[b] Number of patients with first outcome

[c] For this analysis person-time is from first entry to therapy cohort entry until end of observation

Figure D3.SE Cumulative incidence (with 95% C.I.) of CRC in the population of unique study persons since entry to initial therapy cohort.

Note: The corresponding Kaplan-Meier plot cannot be shown, as otherwise stated in the SAP due to the Danish implementation of the GDPR.

Number of patients included:	7,469
Number of CRC cases:	41
Person-years, total:	28,261.2
Person-years, mean:	3.8
Person-years, min, max:	N.P.
Rate per 1,000 (with 95% CI)	1.5 (1.0, 2.0)

Abbreviations: CI: confidence interval; CRC: colorectal cancer; GDPR: General data protection regulation; N.P.: not permissible; SAP: Statistical Analysis Plan

Figure D4.SE Cumulative incidence of first occurrence of all-cause TC in the population of unique study persons since entry to initial therapy cohort.

Note: The corresponding Kaplan-Meier plot cannot be shown, as otherwise stated in the SAP due to the Danish implementation of the GDPR.

Number of patients included:	7,469
Number of total colectomies:	474
Person-years, total:	26,863.3
Person-years, mean:	3.6
Person-years, min, max):	N.P.
Rate per 1,000 (with 95% CI)	17.6 (16.1, 19.3)

Abbreviations: CI: confidence interval; CRC: colorectal cancer; GDPR: General data protection regulation; N.P.: not permissible; SAP: Statistical Analysis Plan; TC: total colectomy;

B. Main association analyses

Table P1A.DK Poisson regression analysis of CRC as the outcome. GLM versus Other Anti-TNF.

	Number N	Person-years PY[a]	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	Other Anti-TNF (ref)
Therapy				**N.P.**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.		
Other Anti-TNF	N.P.	N.P.	N.P.		
Age at therapy[d]				**N.P.**	**1.0 (ref.)**
<35	<5	N.P.	N.P.		
≥35	N.P.	N.P.	N.P.		
Sex				**N.P.**	**1.0 (ref.)**
Male	N.P.	N.P.	N.P.		
Female	<5	N.P.	N.P.		
Calendar year of therapy[d]				**N.P.**	**1.0 (ref.)**
2013-2017	5	4,013.7	1.2 (0.5, 3.0)		
>=2018	8	10,061.5	0.8 (0.4, 1.6)		
UC duration (from first UC diagnosis until therapy) in years[d]				**N.P.**	**1.0 (ref.)**
0-4	<5	N.P.	N.P.		
5-9	<5	N.P.	N.P.		
≥10	9	4,641.7	1.9 (1.0, 3.7)		
Maximum extent of disease recorded since first UC diagnosis through therapy cohort entry				**N.P.**	**1.0 (ref.)**
E1: Ulcerative proctitis	<5	N.P.	N.P.		
E2: Left sided UC (distal UC)	<5	N.P.	N.P.		
E3: Extensive UC (pancolitis)	N.P.	N.P.	N.P.		
Unclassifiable extent	<5	N.P.	N.P.		
≥2 registrations of systemic steroid use in 12 months prior to therapy				**N.P.**	**1.0 (ref.)**

	Number N	Person-years PY[a]	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	Other Anti-TNF (ref)
No	7	10,728.2	0.7 (0.3, 1.4)		
Yes	6	3,347.0	1.8 (0.8, 4.0)		
Prior diagnosis[e] with sclerosing cholangitis				**N.P.**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis[e] with arthropathies				**N.P.**	**1.0 (ref.)**
No	13	13,983.2	0.9 (0.5, 1.6)		
Yes	0	92.0	0.0 (0.0, 0.0)		
Prior diagnosis[e] with psoriasis				**N.P.**	**1.0 (ref.)**
No	13	13,556.5	1.0 (0.6, 1.7)		
Yes	0	518.7	0.0 (0.0, 0.0)		
Prior diagnosis[e] with Crohn's Disease				**N.P.**	**1.0 (ref.)**
No	8	9,937.0	0.8 (0.4, 1.6)		
Yes	5	4,138.3	1.2 (0.5, 2.9)		
Number of colonoscopies and/or sigmoidoscopies in 12 months prior to therapy				**N.P.**	**1.0 (ref.)**
0	5	7,653.9	0.7 (0.3, 1.6)		
1	<5	N.P.	N.P.		
≥2	<5	N.P.	N.P.		
Prior therapy with TP				**N.P.**	**1.0 (ref.)**
No	<5	N.P.	N.P.		
Yes	N.P.	N.P.	N.P.		
Use of biologic agents (including IFX, ADA, GLM, VEDO, other biologics) prior to therapy				**N.P.**	**1.0 (ref.)**
No	13	13,526.3	1.0 (0.6, 1.7)		
Yes	0	548.9	0.0 (0.0, 0.0)		
Adjusted: Model including variables from DAG				**N.P.**	**1.0 (ref.)**
Adjusted: Final model				**N.P.**	**1.0 (ref.)**

Abbreviations: ADA: adalimumab; CI: confidence interval; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, history of sclerosing cholangitis

[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, history of CD, history of therapy with TP, and history of therapy with biologics

Notes:

- Covariates were updated continuously. For further details of covariates, see Text Table 7
- GLM risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up.; (6) 1 day after registered start of therapy with Other Anti-TNF study drugs
- Other Anti-TNF risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up; (6) 1 day after registered start of therapy with GLM
- Note: Overlap risk window (GLM + Other Anti-TNF) starts 1 day after registered start of therapy with a second Anti-TNF study drug (ie. drug A = GLM followed by Other Anti-TNF = drug B, or drug A = Other Anti-TNF followed by GLM = drug B). The Overlap risk window ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Total colectomy for CRC as the outcome; (5) Date of last follow-up. Due to small numbers the overlap risk windows have been grouped with the GLM risk windows

Table P1B.DK Poisson regression analysis of CRC as the outcome. GLM versus TP.

	Number N	Person-years PY[a]	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (95% CI)	TP (ref.)
Therapy				**N.P.**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.		
TP	N.P.	N.P.	N.P.		
Age at therapy[d]				**N.P.**	**1.0 (ref.)**
<35	<5	N.P.	N.P.		
≥35	N.P.	N.P.	N.P.		
Sex				**N.P.**	**1.0 (ref.)**
Male	N.P.	N.P.	N.P.		
Female	<5	N.P.	N.P.		
Calendar year of therapy[d]				**N.P.**	**1.0 (ref.)**
2013-2017	<5	N.P.	N.P.		
>=2018	N.P.	N.P.	N.P.		
UC duration (from first UC diagnosis until therapy) in years[d]				**N.P.**	**1.0 (ref.)**
0-4	<5	N.P,	N.P.		
5-9	<5	N.P.	N.P.		
≥10	N.P.	N.P.	N.P.		
Maximum extent of disease recorded since first UC diagnosis through therapy cohort entry				**N.P.**	**1.0 (ref.)**
E1: Ulcerative proctitis	<5	N.P.	N.P.		
E2: Left sided UC (distal UC)	<5	N.P,	N.P.		
E3: Extensive UC (pancolitis)	N.P.	N.P.	N.P.		
Unclassifiable extent	<5	N.P.	N.P.		
≥2 registrations of systemic steroid use in 12 months prior to therapy				**N.P.**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis[e] with sclerosing cholangitis				**N.P.**	**1.0 (ref.)**

	Number N	Person-years PY[a]	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (95% CI)	TP (ref.)
No	9	8,485.5	1.1 (0.6, 2.0)		
Yes	0	167.4	0.0 (0.0, 0.0)		
Prior diagnosis[e] with arthropathies				**N.P.**	**1.0 (ref.)**
No	9	8,605.6	1.0 (0.5, 2.0)		
Yes	0	47.2	0.0 (0.0, 0.0)		
Prior diagnosis[e] with psoriasis				**N.P.**	**1.0 (ref.)**
No	9	8,532.9	1.1 (0.5, 2.0)		
Yes	0	119.9	0.0 (0.0, 0.0)		
Prior diagnosis[e] with Crohn's Disease				**N.P.**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Number of colonoscopies and/or sigmoidoscopies in 12 months prior to therapy				**N.P.**	**1.0 (ref.)**
0	N.P.	N.P.	N.P.		
1	<5	N.P.	N.P.		
≥2	<5	N.P.	N.P.		
Prior therapy with TP				**N.A.**	**N.A.**
No	0	338.2	0.0 (0.0, 0.0)		
Yes	9	8,314.6	1.1 (0.6, 2.1)		
Use of biologic agents[e] (including IFX, ADA, GLM, VEDO, other biologics) prior to therapy				**N.A.**	**N.A.**
No	9	8,135.4	1.1 (0.6, 2.1)		
Yes	0	517.4	0.0 (0.0, 0.0)		
Adjusted: Model including variables from DAG				**N.P.**	**1.0 (ref.)**
Adjusted: Final model				**N.P.**	**1.0 (ref.)**

Abbreviations: ADA: adalimumab; CI: confidence interval; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.A.: not applicable; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio
[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, histories of sclerosing cholangitis
[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, and history of CD
[d] Use of biologic agents prior to cohort entry which was updated during follow-up after cohort entry

Notes:

- Covariates are updated continuously. For further details of covariates, see Text Table 7
- GLM risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up. In this comparison therapys with Other Anti-TNF study drugs are not considered; accordingly, overlapping risk windows with Other Anti-TNF are attributable to GLM
- TP risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) outcome of interest; (4) All-cause TC; (5) Date of last follow-up; (6) 1 day after registered start of therapy with GLM or Other Anti-TNF

Table P2A.DK Poisson regression analysis of all-cause TC as the outcome. GLM versus Other Anti-TNF.

	Number N	Person-years PY[a]	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	Other Anti-TNF (ref)
Therapy				**1.5 (1.2, 1.9)**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)		
Other Anti-TNF	410	7,646.2	53.6 (48.7, 59.1)		
Age at therapy[d]				**1.5 (1.2, 1.9)**	**1.0 (ref.)**
<35	243	3,767.3	64.5 (56.9, 73.1)		
≥35	252	4,955.3	50.9 (44.9, 57.5)		
Sex				**1.5 (1.2, 1.9)**	**1.0 (ref.)**
Male	251	4,389.7	57.2 (50.5, 64.7)		
Female	244	4,333.0	56.3 (49.7, 63.8)		
Calendar year of therapy[d]				**1.5 (1.2, 1.9)**	**1.0 (ref.)**
2013-2017	298	3,074.1	96.9 (86.5, 108.6)		
>=2018	197	5,648.5	34.9 (30.3, 40.1)		
UC duration (from first UC diagnosis until therapy) in years[d]				**1.7 (1.3, 2.2)**	**1.0 (ref.)**
0-4	342	3,899.0	87.7 (78.9, 97.5)		
5-9	65	2,173.3	29.9 (23.5, 38.1)		
≥10	88	2,650.4	33.2 (26.9, 40.9)		
Maximum extent of disease recorded since first UC diagnosis through therapy cohort entry				**1.4 (1.1, 1.8)**	**1.0 (ref.)**
E1: Ulcerative proctitis	8	412.2	19.4 (9.7, 38.8)		
E2: Left sided UC (distal UC)	21	724.0	29.0 (18.9, 44.5)		
E3: Extensive UC (pancolitis)	433	6,202.3	69.8 (63.5, 76.7)		
Unclassifiable extent	33	1,384.1	23.8 (17.0, 33.5)		
≥2 registrations of systemic steroid use in 12 months prior to therapy				**1.5 (1.2, 1.9)**	**1.0 (ref.)**
No	286	6,252.5	45.7 (40.7, 51.4)		
Yes	209	2,470.1	84.6 (73.9, 96.9)		
Prior diagnosis[e] with sclerosing cholangitis				**1.5 (1.2, 1.9)**	**1.0 (ref.)**

	Number N	Person-years PY[a]	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	Other Anti-TNF (ref)
No	484	8,584.0	56.4 (51.6, 61.6)		
Yes	11	138.7	79.3 (43.9, 143.2)		
Prior diagnosis[e] with arthropathies				**N.P.**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis[e] with psoriasis				**1.5 (1.2, 1.9)**	**1.0 (ref.)**
No	484	8,409.3	57.6 (52.6, 62.9)		
Yes	11	313.3	35.1 (19.4, 63.4)		
Prior diagnosis[e] with Crohn's Disease				**1.4 (1.1, 1.7)**	**1.0 (ref.)**
No	408	6,108.6	66.8 (60.6, 73.6)		
Yes	87	2,614.0	33.3 (27.0, 41.1)		
Number of colonoscopies and/or sigmoidoscopies in 12 months prior to therapy				**1.5 (1.2, 1.9)**	**1.0 (ref.)**
0	193	4,292.1	45.0 (39.0, 51.8)		
1	129	2,534.9	50.9 (42.8, 60.5)		
≥2	173	1,895.7	91.3 (78.6, 105.9)		
Prior therapy with TP				**1.5 (1.2, 1.9)**	**1.0 (ref.)**
No	199	1,949.0	102.1 (88.9, 117.3)		
Yes	296	6,773.7	43.7 (39.0, 49.0)		
Use of biologic agents (including IFX, ADA, GLM, VEDO, other biologics) prior to therapy				**1.3 (1.0, 1.7)**	**1.0 (ref.)**
No	293	5,668.0	51.7 (46.1, 58.0)		
Yes	202	3,054.6	66.1 (57.6, 75.9)		
Adjusted: Model including variables from DAG				**1.3 (1.0, 1.7)**	**1.0 (ref.)**
Adjusted: Final model				**1.3 (1.0, 1.6)**	**1.0 (ref.)**

Abbreviations: ADA: adalimumab; CI: confidence interval; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Person-years calculated using 90 day extended risk window as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, history of sclerosing cholangitis, history of therapy with steroids, and history of therapy with biologics
[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, history of CD, history of therapy with TP, and history of therapy with biologics. History of arthropathies was excluded due to lack of data in the Danish data set

Notes:

- Covariates were updated continuously. For further details of covariates, see Text Table 7
- GLM risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up.; (5) 1 day after registered start of therapy with Other Anti-TNF study drugs
- Other Anti-TNF risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up; (5) 1 day after registered start of therapy with GLM
- Note: Overlap risk window (GLM + Other Anti-TNF) starts 1 day after registered start of therapy with a second Anti-TNF study drug (ie. drug A = GLM followed by Other Anti-TNF = drug B, or drug A = Other Anti-TNF followed by GLM = drug B). The Overlap risk window ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up. Due to small numbers the overlap risk windows have been grouped with the GLM risk windows

Table P2B.DK Poisson regression analysis of all-cause TC as the outcome. GLM versus TP.

	Number N	Person-years PY[a]	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (95% CI)	TP (ref.)
Therapy				**10.4 (6.7, 16.0)**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)		
TP	27	3,540.9	7.6 (5.2, 11.1)		
Age at therapy[d]				**10.5 (6.8, 16.2)**	**1.0 (ref.)**
<35	46	1,909.8	24.1 (18.0, 32.2)		
≥35	66	2,707.5	24.4 (19.2, 31.0)		
Sex				**10.3 (6.7, 15.8)**	**1.0 (ref.)**
Male	48	2,358.9	20.3 (15.3, 27.0)		
Female	64	2,258.4	28.3 (22.2, 36.2)		
Calendar year of therapy[d]				**11.7 (7.6, 18.1)**	**1.0 (ref.)**
2013-2017	72	1,875.8	38.4 (30.5, 48.4)		
>=2018	40	2,741.5	14.6 (10.7, 19.9)		
UC duration (from first UC diagnosis until therapy) in years[d]				**13.2 (8.5, 20.6)**	**1.0 (ref.)**
0-4	72	2,358.7	30.5 (24.2, 38.5)		
5-9	13	2,173.3	6.0 (3.5, 10.3)		
≥10	26	1,126.3	23.1 (15.7, 33.9)		
Maximum extent of disease recorded since first UC diagnosis through therapy cohort entry				**N.P.**	**1.0 (ref.)**
E1: Ulcerative proctitis	<5	N.A.	N.P.		
E2: Left sided UC (distal UC)	10	547.0	18.3 (9.8, 34.0)		
E3: Extensive UC (pancolitis)	97	3,124.6	31.0 (25.4, 37.9)		
Unclassifiable extent	<5	N.P.	N.P.		
≥2 registrations of systemic steroid use in 12 months prior to therapy				**11.1 (7.2, 17.1)**	**1.0 (ref.)**
No	57	3,254.0	17.5 (13.5, 22.7)		
Yes	55	1,363.3	40.3 (31.0, 52.5)		
Prior diagnosis[e] with sclerosing cholangitis				**N.P.**	**1.0 (ref.)**

	Number N	Person-years PY[a]	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (95% CI)	TP (ref.)
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis[e] with arthropathies				**10.5 (6.8, 16.3)**	**1.0 (ref.)**
No	112	4,593.0	24.4 (20.3, 29.3)		
Yes	0	24.3	0.0 (0.0, 0.0)		
Prior diagnosis[e] with psoriasis				**N.P.**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis[e] with Crohn's Disease				**10.3 (6.7, 15.9)**	**1.0 (ref.)**
No	94	3,679.9	25.5 (20.9, 31.3)		
Yes	18	937.4	19.2 (12.1, 30.5)		
Number of colonoscopies and/or sigmoidoscopies in 12 months prior to therapy				**9.7 (6.3, 15.0)**	**1.0 (ref.)**
0	36	2,548.3	14.1 (10.2, 19.6)		
1	36	1,265.0	28.5 (20.5, 39.5)		
≥2	40	804.0	49.8 (36.5, 67.8)		
Prior therapy with TP				**N.A**	**N.A.**
No	13	217.2	59.8 (34.8, 103.1)		
Yes	99	4,400.1	22.5 (18.5, 27.4)		
Use of biologic agents (including IFX, ADA, GLM, VEDO, other biologics) prior to therapy				**N.A.**	**N.A.**
No	30	3,677.7	8.2 (5.7, 11.7)		
Yes	82	939.6	87.3 (70.3, 108.4)		
Adjusted: Model including variables from DAG				**13.6 (8.7, 21.3)**	**1.0 (ref.)**
Adjusted: Final model				**12.7 (8.1, 19.8)**	**1.0 (ref.)**

Abbreviations: ADA: adalimumab; CI: confidence interval; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Person-years calculated using 90 day extended risk window as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio
[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, history of therapy with steroids, history of sclerosing cholangitis
[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of psoriasis, and history of CD. History of arthropathies was excluded due to lack of data in the Danish data set

Notes:

- Covariates were updated continuously. For further details of covariates, see Text Table 7
- GLM risk window starts 1 day after registered start of therapy and ends 90 days after discontinuation *unless* one of the following events occurs before that. In such case the GLM window ends at the first occurring event. These events include (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up. In this comparison therapys with Other Anti-TNF study drugs are not considered; accordingly, overlapping risk windows with Other Anti-TNF are attributable to GLM
- TP risk window starts 1 day after registered start of therapy and ends 90 days after discontinuation unless one of the following events occurs before that. In such case the TP window ends at the first occurring event. These events include (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up; (5) 1 day after registered start of therapy with GLM or Other Anti-TNF

Table P1A.SE Poisson regression analysis of CRC as the outcome. GLM versus Other Anti-TNF.

	Number (N)	Person-years (PY[a])	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	Other Anti-TNF (ref)
Therapy				**N.P.**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.		
Other Anti-TNF	N.P.	N.P.	N.P.		
Age at therapy				**N.P.**	**1.0 (ref.)**
<35	<5	N.P.	N.P.		
>35	N.P.	N.P.	N.P.		
Sex				**N.P.**	**1.0 (ref.)**
Male	11	5,741.6	1.9 (1.1, 3.5)		
Female	9	5,261.6	1.7 (0.9, 3.3)		
Calendar year of therapy				**N.P.**	**1.0 (ref.)**
2013-2017	<5	N.P.	N.P.		
>=2018	N.P.	N.P.	N.P.		
UC duration (from first UC diagnosis until therapy) in years				**N.P.**	**1.0 (ref.)**
0-4	<5	N.P.	N.P.		
5-9	<5	N.P.	N.P.		
≥10	14	4,321.2	3.2 (1.9, 5.5)		
Maximum extent of disease recorded since first UC diagnosis through therapy cohort entry				**N.P.**	**1.0 (ref.)**
E1: Ulcerative proctitis	<5	N.P.	N.P.		
E2: Left sided UC (distal UC)	<5	N.P.	N.P.		
E3: Extensive UC (pancolitis)	15	6,777.6	2.2 (1.3, 3.7)		
Unclassifiable extent	<5	N.P.	N.P.		
≥2 registrations of systemic steroid use in 12 months prior to therapy				**N.P.**	**1.0 (ref.)**
No	14	7,483.4	1.9 (1.1, 3.2)		
Yes	6	3,519.8	1.7 (0.8, 3.8)		
Prior diagnosis with sclerosing cholangitis				**N.P.**	**1.0 (ref.)**
No	<5	N.P.	N.P.		

	Number (N)	Person-years (PY[a])	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	Other Anti-TNF (ref)
Yes	N.P.	N.P.	N.P.		
Prior diagnosis with arthropathies				**N.P.**	**1.0 (ref.)**
No	14	9,817.6	1.4 (0.8, 2.4)		
Yes	6	1,185.5	5.1 (2.3, 11.3)		
Prior diagnosis with psoriasis				**N.P.**	**1.0 (ref.)**
No	<5	N.P.	N.P.		
Yes	N.P.	N.P.	N.P.		
Prior diagnosis with Crohn's Disease				**N.P.**	**1.0 (ref.)**
No	11	6,528.5	1.7 (0.9, 3.0)		
Yes	9	4,474.7	2.0 (1.0, 3.9)		
Number of colonoscopies and/or sigmoidoscopies in 12 months prior to therapy				**N.P.**	**1.0 (ref.)**
0	14	5,927.9	2.4 (1.4, 4.0)		
1	<5	N.P.	N.P.		
>2	<5	N.P.	N.P.		
Prior therapy with TP				**N.P.**	**1.0 (ref.)**
No	7	2,221.5	3.2 (1.5, 6.6)		
Yes	13	8,781.6	1.5 (0.9, 2.5)		
Use of biologic agents (including IFX, ADA, GLM, VEDO, other biologics) prior to therapy				**N.P.**	**1.0 (ref.)**
No	20	10,863.7	1.8 (1.2, 2.9)		
Yes	0	139.5	0.0 (0.0, 0.0)		
Adjusted: Model including variables from DAG[c]				**N.P.**	**1.0 (ref.)**
Adjusted: Final model[d]				**N.P.**	**1.0 (ref.)**

Abbreviations: ADA: adalimumab; CI: confidence interval; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, history of sclerosing cholangitis

[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, history of CD, history of therapy with TP, and history of therapy with biologics

Notes:

- Covariates were updated continuously. For further details of covariates, see Text Table 7
- GLM risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up.; (6) 1 day after registered start of therapy with Other Anti-TNF study drugs
- Other Anti-TNF risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up; (6) 1 day after registered start of therapy with GLM
- Note: Overlap risk window (GLM + Other Anti-TNF) starts 1 day after registered start of therapy with a second Anti-TNF study drug (ie. drug A = GLM followed by Other Anti-TNF = drug B, or drug A = Other Anti-TNF followed by GLM = drug B). The Overlap risk window ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Total colectomy for CRC as the outcome; (5) Date of last follow-up. Due to small numbers the overlap risk windows have been grouped with the GLM risk windows

Table P1B.SE Poisson regression analysis of CRC as the outcome. GLM versus TP.

	Number (N)	Person-years (PY[a])	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	TP (ref)
Therapy				**N.P.**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.		
TP	N.P.	N.P.	N.P.		
Age at therapy				**N.P.**	**1.0 (ref.)**
<35	<5	N.P.	N.P.		
≥35	N.P.	N.P.	N.P.		
Sex				**N.P.**	**1.0 (ref.)**
Male	9	9,343.8	1.0 (0.5, 1.9)		
Female	11	7,642.7	1.4 (0.8, 2.6)		
Calendar year of therapy				**N.P.**	**1.0 (ref.)**
2013-2017	9	6,433.4	1.4 (0.7, 2.7)		
≥2018	11	10,553.1	1.0 (0.6, 1.9)		
UC duration (from first UC diagnosis until therapy) in years				**N.P.**	**1.0 (ref.)**
0-4	<5	N.P.	N.P.		
5-9	N.P.	N.P.	N.P.		
≥10	10	4,381.5	2.3 (1.2, 4.2)		
Maximum extent of disease recorded since first UC diagnosis through therapy cohort entry				**N.P.**	**1.0 (ref.)**
E1: Ulcerative proctitis	<5	N.P.	N.P.		
E2: Left sided UC (distal UC)	<5	N.P.	N.P.		
E3: Extensive UC (pancolitis)	13	9,564.4	1.4 (0.8, 2.3)		
Unclassifiable extent	<5	N.P.	N.P.		
≥2 registrations of systemic steroid use in 12 months prior to therapy				**N.P.**	**1.0 (ref.)**
No	10	11,489.6	0.9 (0.5, 1.6)		
Yes	10	5,497.0	1.8 (1.0, 3.4)		

	Number (N)	Person-years (PY[a])	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	TP (ref)
Prior diagnosis with sclerosing cholangitis				**N.P.**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis with arthropathies				**N.P.**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis with psoriasis				**N.P.**	**1.0 (ref.)**
No	20	16,833.3	1.2 (0.8, 1.8)		
Yes	0	153.2	0.0 (0.0, 0.0)		
Prior diagnosis with Crohn's Disease				**N.P.**	**1.0 (ref.)**
No	11	12,891.7	0.9 (0.5, 1.5)		
Yes	9	4,094.8	2.2 (1.1, 4.2)		
Number of colonoscopies and/or sigmoidoscopies in 12 months prior to therapy				**N.P.**	**1.0 (ref.)**
0	10	9,848.0	1.0 (0.5, 1.9)		
1	N.P.	N.P.	N.P.		
≥2	<5	N.P.	N.P.		
Prior therapy with TP				**N.A.**	**1.0 (ref.)**
No	<5	N.P.	N.P.		
Yes	N.P.	N.P.	N.P.		
Use of biologic agents (including IFX, ADA, GLM, VEDO, other biologics) prior to therapy				**N.A.**	**1.0 (ref.)**
No	20	16,856.2	1.2 (0.8, 1.8)		
Yes	0	130.3	0.0 (0.0, 0.0)		
Adjusted: Model including variables from DAG[c]				**N.P.**	**1.0 (ref.)**
Adjusted: Final model[d]				**N.P.**	**1.0 (ref.)**

Abbreviations: ADA: adalimumab; CI: confidence interval; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.A.: not applicable; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Person-years calculated as outlined Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, histories of sclerosing cholangitis

[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, and history of CD

Notes:

- Covariates are updated continuously. For further details of covariates, see Text Table 7
- GLM risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) All-cause TC; (5) Date of last follow-up. In this comparison, therapies with Other Anti-TNF study drugs are not considered; accordingly, overlapping risk windows with Other Anti-TNF are attributable to GLM
- TP risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) outcome of interest; (4) All-cause TC; (5) Date of last follow-up; (6) 1 day after registered start of therapy with GLM or Other Anti-TNF

Table P2A.SE Poisson regression analysis of all-cause TC as the outcome. GLM versus Other Anti-TNF.

	Number (N)	Person-years (PY[a])	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	Other Anti-TNF (ref)
Therapy				**1.4 (0.9, 2.3)**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)		
Other Anti-TNF	162	6,094.3	26.6 (22.8, 31.0)		
Age at therapy				**1.5 (1.0, 2.4)**	**1.0 (ref.)**
<35	98	2,992.8	32.7 (26.9, 39.9)		
≥35	85	3,647.2	23.3 (18.8, 28.8)		
Sex				**1.5 (0.9, 2.4)**	**1.0 (ref.)**
Male	118	3,618.5	32.6 (27.2, 39.1)		
Female	65	3,021.5	21.5 (16.9, 27.4)		
Calendar year of therapy				**1.3 (0.8, 2.1)**	**1.0 (ref.)**
2013-2017	111	2,592.9	42.8 (35.5, 51.6)		
≥2018	72	4,047.1	17.8 (14.1, 22.4)		
UC duration (from first UC diagnosis until therapy) in years				**1.7 (1.1, 2.6)**	**1.0 (ref.)**
0-4	109	2,400.8	45.4 (37.6, 54.8)		
5-9	37	1,807.6	20.5 (14.8, 28.3)		
≥10	37	2,431.6	15.2 (11.0, 21.0)		
Maximum extent of disease recorded since first UC diagnosis through therapy cohort entry				**1.3 (0.8, 2.1)**	**1.0 (ref.)**
E1: Ulcerative proctitis	<5	N.P.	N.P.		
E2: Left sided UC (distal UC)	N.P.	N.P.	N.P.		
E3: Extensive UC (pancolitis)	160	3,974.0	40.3 (34.5, 47.0)		
Unclassifiable extent	14	1,131.0	12.4 (7.3, 20.9)		
≥2 registrations of systemic steroid use in 12 months prior to therapy				**1.4 (0.9, 2.2)**	**1.0 (ref.)**
No	73	4,429.2	16.5 (13.1, 20.7)		
Yes	110	2,210.9	49.8 (41.3, 60.0)		

	Number (N)	Person-years (PY[a])	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (incl. Overlap) (95% CI)	Other Anti-TNF (ref)
Prior diagnosis with sclerosing cholangitis				**1.4 (0.9, 2.3)**	**1.0 (ref.)**
No	175	6,352.6	27.5 (23.8, 31.9)		
Yes	8	287.4	27.8 (13.9, 55.7)		
Prior diagnosis with arthropathies				**1.5 (1.0, 2.4)**	**1.0 (ref.)**
No	174	5,901.1	29.5 (25.4, 34.2)		
Yes	9	739.0	12.2 (6.3, 23.4)		
Prior diagnosis with psoriasis				**1.4 (0.9, 2.3)**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis with Crohn's Disease				**1.4 (0.9, 2.2)**	**1.0 (ref.)**
No	128	4,063.3	31.5 (26.5, 37.5)		
Yes	55	2,576.7	21.3 (16.4, 27.8)		
Number of colonoscopies and/or sigmoidoscopies in 12 months prior to therapy				**1.3 (0.8, 2.1)**	**1.0 (ref.)**
0	58	3,542.5	16.4 (12.7, 21.2)		
1	47	1,880.8	25.0 (18.8, 33.3)		
≥2	78	1,216.7	64.1 (51.4, 80.0)		
Prior therapy with TP				**1.5 (0.9, 2.3)**	**1.0 (ref.)**
No	33	1,484.5	22.2 (15.8, 31.3)		
Yes	150	5,155.5	29.1 (24.8, 34.1)		
Use of biologic agents (including IFX, ADA, GLM, VEDO, other biologics) prior to therapy				**1.3 (0.8, 2.1)**	**1.0 (ref.)**
No	144	5,595.5	25.7 (21.9, 30.3)		
Yes	39	1,044.5	37.3 (27.3, 51.1)		
Adjusted: Model including variables from DAG[c]				**1.2 (0.7, 1.9)**	**1.0 (ref.)**
Adjusted: Final model[d]				**1.1 (0.7, 1.8)**	**1.0 (ref.)**

Abbreviations: ADA: adalimumab; CI: confidence interval; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Person-years calculated using 90 day extended risk window as outlined in Section 9.8.2 and SAP, Section 6.3.4
[b] IRR: Incidence Rate Ratio
[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, history of sclerosing cholangitis, history of therapy with steroids, and history of therapy with biologics
[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of arthropathies, history of psoriasis, history of CD, history of therapy with TP, and history of therapy with biologics. History of arthropathies was excluded due to lack of data in the Danish data set

Notes:

- Covariates were updated continuously. For further details of covariates, see Text Table 7
- GLM risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up.; (5) 1 day after registered start of therapy with Other Anti-TNF study drugs
- Other Anti-TNF risk window starts 1 day after registered start of therapy and ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up; (5) 1 day after registered start of therapy with GLM
- Note: Overlap risk window (GLM + Other Anti-TNF) starts 1 day after registered start of therapy with a second Anti-TNF study drug (ie. drug A = GLM followed by Other Anti-TNF = drug B, or drug A = Other Anti-TNF followed by GLM = drug B). The Overlap risk window ends at the first occurring event among the following: (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up. Due to small numbers the overlap risk windows have been grouped with the GLM risk windows

Table P2B.SE Poisson regression analysis of all-cause TC as the outcome. GLM versus TP.

	Number (N)	Person-years (PY[a])	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (95% CI)	TP (ref.)
Therapy				**4.4 (2.7, 7.0)**	**1.0 (ref.)**
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)		
TP	92	10,455.1	8.8 (7.2, 10.8)		
Age at therapy[d]				**4.4 (2.7, 7.1)**	**1.0 (ref.)**
<35	55	5,532.7	9.9 (7.6, 12.9)		
≥35	58	5,468.1	10.6 (8.2, 13.7)		
Sex				**4.6 (2.9, 7.5)**	**1.0 (ref.)**
Male	79	6,243.2	12.7 (10.1, 15.8)		
Female	34	4,757.6	7.1 (5.1, 10.0)		
Calendar year of therapy				**4.2 (2.6, 6.8)**	**1.0 (ref.)**
2013-2017	66	4,644.3	14.2 (11.2, 18.1)		
≥2018	47	6,356.5	7.4 (5.6, 9.8)		
UC duration (from first UC diagnosis until therapy) in years				**5.6 (3.4, 9.2)**	**1.0 (ref.)**
0-4	78	6,296.8	12.4 (9.9, 15.5)		
5-9	15	2,343.4	6.4 (3.9, 10.6)		
≥10	20	2,360.6	8.5 (5.5, 13.1)		
Maximum extent of disease recorded since first UC diagnosis through therapy cohort entry				**3.9 (2.4, 6.2)**	**1.0 (ref.)**
E1: Ulcerative proctitis	6	584.4	10.3 (4.6, 22.9)		
E2: Left sided UC (distal UC)	7	2,541.5	2.8 (1.3, 5.8)		
E3: Extensive UC (pancolitis)	95	6,238.2	15.2 (12.5, 18.6)		
Unclassifiable extent	5	1,636.8	3.1 (1.3, 7.3)		
≥2 registrations of systemic steroid use in 12 months prior to therapy				**4.3 (2.7, 6.9)**	**1.0 (ref.)**
No	53	7,233.7	7.3 (5.6, 9.6)		
Yes	60	3,767.1	15.9 (12.4, 20.5)		

	Number (N)	Person-years (PY[a])	Crude Incidence rate per 1000 PY (95% CI)	IRR[b]	
				GLM (95% CI)	TP (ref.)
Prior diagnosis with sclerosing cholangitis				**4.3 (2.7, 6.9)**	**1.0 (ref.)**
No	104	10,547.0	9.9 (8.1, 12.0)		
Yes	9	453.7	19.8 (10.3, 38.1)		
Prior diagnosis with arthropathies				**5.2 (3.2, 8.4)**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis with psoriasis				**4.4 (2.7, 7.0)**	**1.0 (ref.)**
No	N.P.	N.P.	N.P.		
Yes	<5	N.P.	N.P.		
Prior diagnosis with Crohn's Disease				**4.4 (2.7, 7.0)**	**1.0 (ref.)**
No	86	8,592.5	10.0 (8.1, 12.4)		
Yes	27	2,408.3	11.2 (7.7, 16.3)		
Number of colonoscopies and/or sigmoidoscopies in 12 months prior to therapy				**3.7 (2.3, 6.0)**	**1.0 (ref.)**
0	38	6,160.5	6.2 (4.5, 8.5)		
1	22	3,044.9	7.2 (4.8, 11.0)		
≥2	53	1,795.5	29.5 (22.6, 38.6)		
Prior therapy with TP				**N.A.**	**N.A.**
No	0	135.5	0.0 (0.0, 0.0)		
Yes	113	10,865.3	10.4 (8.6, 12.5)		
Use of biologic agents (including IFX, ADA, GLM, VEDO, other biologics) prior to therapy				**N.A.**	**N.A.**
No	100	10,721.7	9.3 (7.7, 11.3)		
Yes	13	279.1	46.6 (27.0, 80.2)		
Adjusted: Model including variables from DAG[c]				**4.5 (2.7, 7.4)**	**1.0 (ref.)**
Adjusted: Final model[d]				**3.9 (2.3, 6.4)**	**1.0 (ref.)**

Abbreviations: ADA: adalimumab; CI: confidence interval; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; NF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis; VEDO: vedolizumab

[a] Person-years calculated using 90 day extended risk window as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] The following covariates were included in the model adjusted according to the DAG conclusion: Age, disease duration, calendar year, extent of UC, history of therapy with steroids, history of sclerosing cholangitis

[d] The following covariates were included in the model adjusted for the full set of confounders: Sex, age, disease duration, calendar year, extent of UC, history of lower endoscopies, history of therapy with steroids, history of sclerosing cholangitis, history of psoriasis, and history of CD. History of arthropathies was excluded due to lack of data in the Danish data set

Notes:

- Covariates were updated continuously. For further details of covariates, see Text Table 7
- GLM risk window starts 1 day after registered start of therapy and ends 90 days after discontinuation *unless* one of the following events occurs before that. In such case the GLM window ends at the first occurring event. These events include (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up. In this comparison therapies with Other Anti-TNF study drugs are not considered; accordingly, overlapping risk windows with Other Anti-TNF are attributable to GLM
- TP risk window starts 1 day after registered start of therapy and ends 90 days after discontinuation unless one of the following events occurs before that. In such case the TP window ends at the first occurring event. These events include (1) Death; (2) Emigration; (3) Outcome of interest; (4) Date of last follow-up; (5) 1 day after registered start of therapy with GLM or Other Anti-TNF

C. Sensitivity analyses

Table S1.DK All-cause TC as the outcome: Sensitivity analyses related to therapy switches.

S1A.DK: Following all patients from one day after drug initiation until 90 days after discontinuation or until one of general triggers for end of follow-up. Stratification is based on person-time and corresponding number of outcomes as updated by history of therapy with biologics during the study period.

Outcome: All-cause TC	**Number**	**Person-years (PY[a])**	**Incidence rate (per 1,000 PY)**	**Primary: IRR[b]**			**Sensitivity: IRR[b]**		
Therapy: GLM versus Other Anti-TNF				**Crude**	**Adjusted, DAG[c]**	**Adjusted, FULL[c]**	**Crude**	**Adjusted, DAG[c]**	**Adjusted, FULL[c]**
Primary analysis without stratification									
GLM (incl. overlap with Other Anti-TNF)	85	1,076,5	79.0 (63.8, 97.7)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	N. A. (this part of the analysis is identical with the primary analysis)		
Other Anti-TNF (ref.)	410	7,646.2	53.6 (48.7, 59.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)			
Stratification: No biologic prior to therapy[d]									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Stratification: One or more biologics prior to therapy[e]									
GLM (incl. overlap with Other Anti-TNF)	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See table P2A.DK

[d] Outcomes and person-years accrued until a second type of biologic therapy is initiated

[e] Outcomes and person-years accrued from the day after initiation of second type of biologic therapy

S1B.DK: *Analysis B (p.24)*: Following all patients from one day after drug initiation until 90 days after discontinuation or until one of general triggers for end of follow-up, but overlap period is not attributed to the new drug after a switch, overlapping period is only attributed to the old drug.

Outcome: All-cause TC	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
Therapy: GLM versus Other Anti-TNF				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
GLM	66	986.4	66.9 (52.6, 85.2)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.2 (0.9, 1.6)	1.1 (0.8, 1.4)	1.0 (0.8, 1.4)
Other Anti-TNF (ref.)	429	7,736.3	55.5 (50.4, 61.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See table P2A.DK

S1C.DK: *Analysis C (p. 24)*: Applying a 90-day lag period for all new drug starts regardless of switching.

Outcome: All-cause TC	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
Therapy: GLM versus Other Anti-TNF				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
GLM	56	911.8	61.4 (47.3, 79.8)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	2.1 (1.5, 2.8)	1.1 (0.8, 1.6)	1.2 (0.9, 1.6)
Other Anti-TNF (ref.)	196	6,578.5	29.8 (25.9, 34.3)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See table P2A.DK

Table S2.DK Sensitivity analysis for both colorectal cancer and all-cause TC outcomes. Restricting to patients with two independent registrations of UC as the primary diagnosis and no registrations of CD as a primary or secondary diagnosis. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF)	68	847.5	80.2 (63.3, 101.8)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)
Other Anti-TNF (ref.)	321	4,932.0	65.1 (58.3, 72.6)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	68	847.5	80.2 (63.3, 101.8)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	10.0 (6.1, 16.2)	13.5 (8.2, 22.2)	12.7 (7.7, 21.0)
TP (ref.)	21	2,605.9	8.1 (5.3, 12.4)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CD: Crohn's disease; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years: TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S3.DK Denmark only. Sensitivity analysis for both CRC and all-cause TC outcomes. Restricting to patients without high-level therapy codes.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF)	73	918,9	79.4 (63.2, 99.9)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.4 (1.1, 1.8)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)
Other Anti-TNF (ref.)	383	6772,8	56.5 (51.1, 62.5)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	73	918,9	79.4 (63.2, 99.9)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	10.5 (6.7, 16.5)	13.5 (8.5, 21.4)	12.3 (7.7, 19.6)
TP (ref.)	26	3446,1	7.5 (5.1, 11.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S4.DK Sensitivity analysis: CRC as the outcome. Subsequent PY and events attribute to both TP and GLM therapy cohorts after switching from TP to GLM. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S5A.DK Sensitivity analysis: CRC as the outcome. All therapy cohorts. Risk window starts 6 months after first exposure and ends 6 months after exposure discontinuation. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S5B.DK Sensitivity analysis: CRC as the outcome. All therapy cohorts. Risk window starts 6 months after first exposure and ends 2 years after exposure discontinuation. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S6.DK Sensitivity analysis: CRC as the outcome. All therapy cohorts. Any type (e.g. partial or total) of colectomy will qualify as a censoring event. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S7A.DK Sensitivity analysis: All-cause TC as the outcome. All therapy cohorts. Alternative specification of risk window. Risk window starts one day after therapy start and ends at 6 months after last therapy or until one of the general triggers for end of follow-up. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF)	94	1,196.0	78.6 (64.2, 96.2)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.5 (1.2, 1.9)	1.2 (1.0, 1.6)	1.2 (1.0, 1.6)
Other Anti-TNF (ref.)	432	8,167.0	52.9 (48.1, 58.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	94	1,196.0	78.6 (64.2, 96.2)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	10.0 (6.7, 15.0)	13.0 (8.6, 19.8)	12.1 (8.0, 18.5)
TP (ref.)	31	3,937.5	7.9 (5.5, 11.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S7B.DK Sensitivity analysis: All-cause TC as the outcome. Alternative specification of risk window for TP cohort only. Risk window starts 90 days after first exposure and ends 90 days after the last therapy or until one of the general triggers for end of follow-up. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	15.8 (9.0, 27.8)	20.3 (11.4, 36.0)	18.8 (10.5, 33.5)
TP (ref.)	14	2,800.5	5.0 (3.0, 8.4)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy compariso.

Table S7C.DK Sensitivity analysis: All-cause TC as the outcome. All therapy cohorts. Alternative specification of risk window. Using all follow-up time after entry of therapy cohort (without restricting to 90-day risk window). All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF)	115	2,001.4	57.5 (47.9, 69.0)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.4 (1.1, 1.7)	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)
Other Anti-TNF (ref.)	508	12,093.1	42.0 (38.5, 45.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	115	2,001.4	57.5 (47.9, 69.0)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	9.3 (6.5, 13.3)	12.6 (8.7, 18.2)	11.7 (8.1, 17.0)
TP (ref.)	41	6,657.2	6.2 (4.5, 8.4)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio.

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S8.DK Sensitivity analysis: CRC as the outcome. Assessing effects of competing risks. No censoring at first all-cause TC. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Figure S1.DK Sensitivity analysis: A composite outcome of all-cause TC, CRC, or death. Assessing effects of competing risks. Cumulative survival using all-cause TC, CRC, or death as a composite outcome. Kaplan-Meier plots for the period from first entry to each therapy cohort[a] through end of observation (see Table S9.DK for the statistical analysis using 90-day risk window).

Note: Due to discretional rules it is not permitted to show the Kaplan-Meier plot. The data underlying the plot are summarized below.

	GLM	Other Anti-TNF	TP
Number of patients included:	595	3,676	2,348
Number composite outcomes:	127	690	274
Person-years, total:	2,003.0	13,377.7	10,283.4
Person-years, mean:	3.4	3.6	4.4
Person-years, (min ; max:	N.P.	N.P.	N.P.
Crude IR per 1,000 (95% CI)	63.4 (52.9, 75.5)	51.6 (47.8, 55.6)	26.6 (23.6, 30.0)

Abbreviations: CI: confidence interval; CRC: colorectal cancer; GLM: golimumab; IR: incidence rate; N.P.: not permissible; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine; N.P.: not permissible

[a] Patients are counted more than once if they enter more than one therapy cohort

Table S9.DK Sensitivity analysis: A joint outcome of all-cause TC, CRC, or death. Assessing effects of competing risks. Using all-cause TC, CRC, or death as a joint outcome and using a 90-day risk window. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Joint outcome: All-cause TC, CRC, or death						
Therapy: GLM versus Other Anti-TNF						
GLM (incl. overlap with Other Anti-TNF)	87	1,076.5	80.8 (65.5, 99.7)	1.4 (1.1, 1.8)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)
Other Anti-TNF (ref.)	440	7,642.1	57.6 (52.4, 63.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP						
GLM (incl. overlap with Other Anti-TNF)	87	1,076.5	80.8 (65.5, 99.7)	5.7 (4.0, 8.2)	8.0 (5.5, 11.6)	7.7 (5.3, 11.2)
TP (ref.)	45	3,539.6	12.7 (9.5, 17.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S10.DK Sensitivity analysis: All-cause TC as the outcome. Assessing effects of competing risks. Risk window was censored at the development of CRC. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)
Other Anti-TNF (ref.)	407	7,642.1	53.3 (48.3, 58.7)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	10.7 (6.9, 16.7)	14.3 (9.1, 22.4)	13.2 (8.4, 20.8)
TP (ref.)	26	3,539.6	7.3 (5.0, 10.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S11A.DK Sensitivity analysis for both CRC and all-cause TC outcomes. For patients with lacking information on extent of UC: Assigning maximal disease extent (E3). All point estimates are presented with 95% confidence interval.
Note: Montreal classification code for maximal extent of disease: E3, extensive UC (pancolitis). ICD10 code: K51.0 (Ulcerative colitis).

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF))	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF))	85	1,076.5	79.0 (63.8, 97.7)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.5 (1.2, 1.9)	1.4 (1.1, 1.8)	1.3 (1.0, 1.7)
Other Anti-TNF (ref.)	410	7,646.2	53.6 (48.7, 59.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	10.4 (6.7, 16.0)	15.1 (9.7, 23.5)	14.0 (8.9, 21.8)
TP (ref.)	27	3,540.9	7.6 (5.2, 11.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine
[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4
[b] IRR: Incidence Rate Ratio
[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S11B.DK Sensitivity analysis for both CRC and all-cause TC outcomes. For patients with lacking information on extent of UC: Assigning minimal disease extent (E1). All point estimates are presented with 95% confidence interval.
Note: Montreal classification code for minimal extent of disease: E1, Ulcerative proctitis. ICD10 code: K51.2 (Ulcerative proctitis).

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.2 (1.0, 1.6)
Other Anti-TNF (ref.)	410	7,646.2	53.6 (48.7, 59.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	85	1,076.5	79.0 (63.8, 97.7)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	10.4 (6.7, 16.0)	13.5 (8.6, 21.0)	12.5 (8.0, 19.6)
TP (ref.)	27	3,540.9	7.6 (5.2, 11.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine
[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4
[b] IRR: Incidence Rate Ratio
[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S12.DK Sensitivity analysis: Both CRC and all-cause TC outcomes. Excluding patients with one or more registrations of therapy with biologics other than GLM, ADA, and IFX. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF)	43	620.9	69.3 (51.4, 93.4)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.2 (0.9, 1.7)	1.4 (0.9, 2.0)	1.3 (0.9, 1.8)
Other Anti-TNF (ref.)	322	5,590.2	57.6 (51.6, 64.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	43	620.9	69.3 (51.4, 93.4)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	8.3 (5.1, 13.4)	12.0 (7.2, 19.9)	11.6 (6.9, 19.3)
TP (ref.)	27	3,233.0	8.4 (5.7, 12.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: ADA: adalimumab; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S13.DK Sensitivity analysis: Both CRC and all-cause TC outcomes. Comparison between GLM and TP cohorts. Restricting the GLM cohort to patients who are TP naïve at therapy cohort entry. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	17	269.0	63.2 (39.3, 101.7)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	8.3 (4.5, 15.2)	12.1 (6.3, 23.2)	9.9 (5.0, 19.6)
TP (ref.)	27	3,540.9	7.6 (5.2, 11.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S14B.DK Validation analysis: CRC as the outcome. Assessment of validity of CRC ascertainment: CRC cases ascertained from Hospital discharge diagnoses (primary analysis) versus CRC cases ascertained from the Danish Cancer Registry Only (sensitivity analysis). Association analyses.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	12	12,076.3	1.0 (0.6, 1.7)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.DK)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	6	6,651.53	0.9 (0.6, 1.7)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S15A.DK Sensitivity analysis: Colectomy for intractable disease as the outcome. Excluding all-cause total colectomies where underlying primary discharge diagnosis is CRC. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF)	84	1,076.5	78.0 (63.0, 96.6)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.5 (1.2, 1.9)	1.3 (1.0, 1.6)	1.2 (1.0, 1.6)
Other Anti-TNF (ref.)	407	7,646.2	53.2 (48.3, 58.7)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	84	1,076.5	78.0 (63.0, 96.6)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	10.6 (6.8, 16.5)	14.2 (9.0, 22.3)	13.1 (8.3, 20.6)
TP (ref.)	26	3,540.9	7.3 (5.0, 10.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S15B.DK Sensitivity analysis: Any colectomy as the outcome. Including any type (e.g. partial or total) of colectomy for any indication as the outcome. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.DK)									
GLM (incl. overlap with Other Anti-TNF)	87	1,074.7	81.0 (65.6, 99.9)	1.5 (1.2, 1.9)	1.3 (1.0, 1.7)	1.3 (1.0, 1.6)	1.4 (1.1, 1.8)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)
Other Anti-TNF (ref.)	437	7,597.2	57.5 (52.4, 63.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.DK)									
GLM (incl. overlap with Other Anti-TNF)	87	1,074.7	81.0 (65.6, 99.9)	10.4 (6.7, 16.0)	13.6 (8.7, 21.3)	12.7 (8.1, 19.8)	8.4 (5.7, 12.5)	11.6 (7.7, 17.5)	10.7 (7.1, 16.3)
TP (ref.)	34	3,533.8	9.6 (6.9, 13.5)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S16.DK Sensitivity analysis: All-cause TC as the outcome. Cases, Pys and crude incidence rates of all-cause TC within and outside 90-day risk window.

Outcome: All-cause TC	Therapy cohort[a]		
	GLM (incl. overlap with Other Anti-TNF) (N=595)	Other Anti-TNF (N=3,676)	TP (N=2,348)
Within 90-day risk window			
n[b]	85	469	142
Person-years, PY[c]	1,685.2	8,920.1	5,942.0
Crude Incidence rate per 1,000 PY	50.4	52.6	23.9
95% Confidence Interval	40.8, 62.4	48.0, 57.6	20.3, 28.2
Outside of 90-day risk window			
n[d]	30	123	48
Person-years, PY[d]	963.8	5,508.5	4,346.3
Crude Incidence rate per 1,000 PY	31.1	22.3	11.0
95% Confidence Interval	21.8, 44.5	18.7, 26.6	8.3, 14.7
All follow-up time			
n[e]	115	592	190
Person-years, PY[e]	2,649.0	14,428.5	10,288.4
Crude Incidence rate per 1,000 PY	43.4	41.0	18.5
95% Confidence Interval	36.2, 52.1	37.9, 44.5	16.0, 21.3

Abbreviations: GLM: golimumab; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patients

[b] Number of patients with first outcome registered within 90-day risk windows

[c] Person-years calculated using 90-day risk window as outlined in Section 9.8.2 and SAP, Section 6.3.4

[d] Number of patients and person-years were outside of 90-day risk window

[e] Number of patients and person-years were calculated using all follow-up time

Table S17.DK Sensitivity analysis: All-cause TC as the outcome. Assessing the effect modification by time period concerning switch from one therapy to the next. All point estimates are presented with 95% confidence interval.

Outcome: All-cause TC		**Colectomy within 90 days**		
Therapy: GLM versus Other Anti-TNF		**Yes**	**No**	**Total**
Short time: Switch where Drug B starts as an overlapping drug	*Drug B: GLM*	N.P.	N.P.	N.P.
	Drug B: Other Anti-TNF	<5	N.P.	N.P.
Longer time: Switch where Drug B does not start as an overlapping drug	*Drug B: GLM*	<5	N.P.	N.P.
	Drug B: Other Anti-TNF	<5	N.P.	N.P.

Abbreviations: GLM: golimumab; N.P.: not permissible; TC: total colectomy; TNF: tumor necrosis factor alpha

Table S1.SE All-cause TC as the outcome: Sensitivity analyses related to drug switches.

S1A.SE: Following all patients from one day after drug initiation until 90 days after discontinuation or until one of general triggers for end of follow-up. Stratification is based on person-time and corresponding number of outcomes as updated by history of therapy with biologics during the study period.

Outcome: All-cause TC	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
Therapy: GLM versus Other Anti-TNF				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Primary analysis without stratification									
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	N.A. (this part of the analysis is identical with the primary analysis)		
Other Anti-TNF (ref.)	162	6,094.3	26.6 (22.8, 31.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)			
Stratification: No biologic prior to therapy[d]									
GLM (incl. overlap with Other Anti-TNF)	8	266.6	30.0 (15.0, 60.0)	1.2 (0.6, 2.4)	1.1 (0.5, 2.2)	1.0 (0.5, 2.0)	1.2 (0.6, 2.4)	1.2 (0.6, 2.4)	1.0 (0.5, 2.1)
Other Anti-TNF (ref.)	136	5,328.9	25.5 (21.6, 30.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Stratification: One or more biologics prior to therapy[e]									
GLM (incl. overlap with Other Anti-TNF)	13	279.1	46.6 (27.0, 80.2)	1.4 (0.7, 2.7)	1.3 (0.6, 2.5)	1.1 (0.6, 2.3)	1.4 (0.7, 2.7)	1.3 (0.7, 2.6)	1.2 (0.6, 2.3)
Other Anti-TNF (ref.)	26	765.4	34.0 (23.1, 49.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.A.: not applicable; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See Table P2A.SE

[d] Outcomes and person-years accrued until a second type of biologic therapy is initiated

[e] Outcomes and person-years accrued from the day after initiation of second type of biologic therapy

S1B.SE: *Analysis B (p.24)*: Following all patients from one day after drug initiation until 90 days after discontinuation or until one of general triggers for end of follow-up, but overlap period is not attributed to the new drug after a switch, overlapping period is only attributed to the old drug.

Outcome: All-cause TC	**Number**	**Person-years (PY[a])**	**Incidence rate (per 1,000 PY)**	**Primary: IRR[b]**			**Sensitivity: IRR[b]**		
Therapy: GLM versus Other Anti-TNF				**Crude**	**Adjusted, DAG[c]**	**Adjusted, FULL[c]**	**Crude**	**Adjusted, DAG[c]**	**Adjusted, FULL[c]**
GLM	18	527.8	34.1 (21.5, 54.1)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.3 (0.8, 2.1)	1.0 (0.6, 1.7)	1.0 (0.6, 1.6)
Other Anti-TNF (ref.)	165	6,112.3	27.0 (23.2, 31.4)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See Table P2A.SE

S1C.SE: *Analysis C (p. 24)*: Applying a 90-day lag period for all new drug starts regardless of switching.

Outcome: All-cause TC	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
Therapy: GLM versus Other Anti-TNF				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
GLM	15	463.6	32.4 (19.5, 53.7)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.5 (0.9, 2.6)	1.1 (0.6, 2.0)	1.0 (0.6, 1.9)
Other Anti-TNF (ref.)	108	5,016.6	21.5 (17.8, 26.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See Table P2A.SE

Table S2.SE Sensitivity analysis for both colorectal cancer and all-cause TC outcomes. Restricting to patients with two independent registrations of UC as the primary diagnosis and no registrations of CD as a primary or secondary diagnosis. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.SE)									
GLM (incl. overlap with Other Anti-TNF)	13	356.6	36.5 (21.2, 62.8)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.2 (0.7, 2.1)	1.0 (0.6, 1.9)	1.0 (0.5, 1.8)
Other Anti-TNF (ref.)	103	3,384.5	30.4 (25.1, 36.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	13	356.6	36.5 (21.2, 62.8)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	4.4 (2.4, 8.1)	4.9 (2.7, 9.2)	4.5 (2.4, 8.4)
TP (ref.)	64	7,790.2	8.2 (6.4, 10.5)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CD: Crohn's disease; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine; UC: ulcerative colitis

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S4.SE Sensitivity analysis: CRC as the outcome. Subsequent PY and events attribute to both TP and GLM therapy cohorts after switching from TP to GLM. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S5A.SE Sensitivity analysis: CRC as the outcome. All therapy cohorts. Risk window starts 6 months after first exposure and ends 6 months after exposure discontinuation. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S5B.SE Sensitivity analysis: CRC as the outcome. All therapy cohorts. Risk window starts 6 months after first exposure and ends 2 years after exposure discontinuation. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S6.SE Sensitivity analysis: CRC as the outcome. All therapy cohorts. Any type (e.g. partial or total) of colectomy will qualify as a censoring event. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S7A.SE Sensitivity analysis: All-cause TC as the outcome. All therapy cohorts. Alternative specification of risk window. Risk window starts one day after therapy start and ends at 6 months after last therapy or until one of the general triggers for end of follow-up. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.SE)									
GLM (incl. overlap with Other Anti-TNF)	22	596.4	36.9 (24.3, 56.0)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.3 (0.8, 2.0)	1.1 (0.7, 1.7)	1.0 (0.6, 1.6)
Other Anti-TNF (ref.)	188	6,552.6	28.7 (24.9, 33.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	22	596.4	36.9 (24.3, 56.0)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	3.8 (2.4, 6.0)	3.8 (2.4, 6.1)	3.2 (2.0, 5.3)
TP (ref.)	110	11,226.2	9.8 (8.1, 11.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S7B.SE Sensitivity analysis: All-cause TC as the outcome. Alternative specification of risk window for TP cohort only. The TP risk window starts 90 days after first exposure and ends 90 days after the last therapy or until one of the general triggers for end of follow-up. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	5.8 (3.5, 9.6)	5.5 (3.3, 9.3)	4.7 (2.7, 7.9)
TP (ref.)	58	8,776.7	6.6 (5.1, 8.5)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S7C.SE Sensitivity analysis: All-cause TC as the outcome. All therapy cohorts. Alternative specification of risk window. Using all follow-up time after entry of therapy cohort (without restricting to 90-day risk window). All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.SE)									
GLM (incl. overlap with Other Anti-TNF)	41	1,142.0	35.9 (26.4, 48.8)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.3 (0.9, 1.8)	1.0 (0.7, 1.5)	1.0 (0.7, 1.4)
Other Anti-TNF (ref.)	280	9,865.6	28.4 (25.2, 31.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	41	1,142.0	35.9 (26.4, 48.8)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	3.7 (2.6, 5.3)	3.7 (2.6, 5.3)	3.2 (2.2, 4.6)
TP (ref.)	153	15,855.7	9.6 (8.2, 11.3)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine.

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S8.SE Sensitivity analysis: CRC as the outcome. Assessing effects of competing risks. No censoring at first all-cause TC. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Figure S1.SE Sensitivity analysis: A composite outcome of all-cause TC, CRC, or death. Assessing effects of competing risks. Cumulative survival using all-cause TC, CRC, or death as a composite outcome. Kaplan-Meier plots for the period from first entry to each therapy cohort[a] through end of observation (see Table S9.SE for the statistical analysis using 90-day risk window).

Note: Due to discretional rules it is not permitted to show the Kaplan-Meier plot. The data underlying the plot are summarized below.

	GLM	Other Anti-TNF	TP
Number of patients included:	298	3,385	5,146
Number composite outcomes:	46	352	387
Person-years, total:	1,141.4	10,318.7	19,021.4
Person-years, mean:	3.8	3.0	3.7
Person-years, (min, max):	N.P.	N.P.	N.P.
Crude IR per 1,000 (95% CI)	40.3 (29.5, 53.8)	34.1 (30.6, 37.9)	20.4 (18.4, 22.5)

Abbreviations: CI: confidence interval; CRC: colorectal cancer; GLM: golimumab; IR: incidence rate; N.P.: not permissible; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine; N.P.: not permissible

[a] Patients are counted more than once if they enter more than one therapy cohort

Table S9.SE Sensitivity analysis: A composite outcome of all-cause TC, CRC, or death. Assessing effects of competing risks. Using all-cause TC, CRC, or death as a joint outcome and using 90-day risk window. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Joint outcome: All-cause TC, CRC, or death						
Therapy: GLM versus Other Anti-TNF						
GLM (incl. overlap with Other Anti-TNF)	22	545.5	40.3 (26.6, 61.3)	1.4 (0.9, 2.1)	1.1 (0.7, 1.7)	1.0 (0.6, 1.6)
Other Anti-TNF (ref.)	182	6,093.9	29.9 (25.8, 34.5)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP						
GLM (incl. overlap with Other Anti-TNF)	22	545.5	40.3 (26.6, 61.3)	3.3 (2.1, 5.2)	2.9 (1.8, 4.6)	2.7 (1.7, 4.3)
TP (ref.)	135	10,450.3	12.9 (10.9, 15.3)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S10.SE Sensitivity analysis: All-cause TC as the outcome. Assessing effects of competing risks. Risk window was censored at the development of CRC. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.SE)									
GLM (incl. overlap with Other Anti-TNF)	21	545.5	38.5 (25.1, 59.0)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.5 (0.9, 2.4)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)
Other Anti-TNF (ref.)	157	6,093.9	25.8 (22.0, 30.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	21	545.5	38.5 (25.1, 59.0)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	4.7 (2.9, 7.5)	5.0 (3.0, 8.3)	4.3 (2.6, 7.2)
TP (ref.)	86	10,450.3	8.2 (6.7, 10.2)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S11A.SE Sensitivity analysis for both CRC and all-cause TC outcomes. For patients with lacking information on extent of UC: Assigning maximal disease extent (E3). All point estimates are presented with 95% confidence interval.
Note: Montreal classification code for maximal extent of disease: E3, extensive UC (pancolitis). ICD10 code: K51.0 (Ulcerative colitis).

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.SE)									
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.4 (0.9, 2.3)	1.2 (0.8, 2.0)	1.1 (0.7, 1.8)
Other Anti-TNF (ref.)	162	6,094.3	26.6 (22.8, 31.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	4.4 (2.7, 7.0)	4.6 (2.8, 7.6)	4.0 (2.4, 6.6)
TP (ref.)	92	10,455.1	8.8 (7.2, 10.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine
[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4
[b] IRR: Incidence Rate Ratio
[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S11B.SE Sensitivity analysis for both CRC and all-cause total outcomes. For patients with lacking information on extent of UC: Assigning minimal disease extent (E1). All point estimates are presented with 95% confidence interval.
Note: Montreal classification code for minimal extent of disease: E1, Ulcerative proctitis. ICD10 code: K51.2 (Ulcerative proctitis).

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.SE)									
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)
Other Anti-TNF (ref.)	162	6,094.3	26.6 (22.8, 31.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	4.4 (2.7, 7.0)	4.6 (2.8, 7.5)	3.9 (2.3, 6.4)
TP (ref.)	92	10,455.1	8.8 (7.2, 10.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine
[a] Person-years calculated as outlined Section 9.8.2 and SAP, Section 6.3.4
[b] IRR: Incidence Rate Ratio
[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S12.SE Sensitivity analysis: Both CRC and all-cause TC outcomes. Excluding patients with one or more registrations of therapies with biologics other than GLM, ADA, and IFX. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.SE)									
GLM (incl. overlap with Other Anti-TNF)	20	505.6	39.6 (25.5, 61.3)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.5 (0.9, 2.4)	1.2 (0.8, 2.1)	1.2 (0.7, 1.9)
Other Anti-TNF (ref.)	151	5,729.4	26.4 (22.5, 30.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	20	505.6	39.6 (25.5, 61.3)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	4.5 (2.7, 7.2)	4.7 (2.9, 7.9)	4.0 (2.4, 6.7)
TP (ref.)	92	10,352.9	8.9 (7.2, 10.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: ADA: adalimumab; CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IFX: infliximab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S13.SE Sensitivity analysis: Both CRC and all-cause TC outcomes. Comparison between GLM and TP cohorts. Restricting the GLM cohort to patients who are TP naïve at therapy cohort entry. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Outcome: All-cause TC									
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	0	144.2	0.0 (0.0, 0.0)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	No fit could be obtained in this model		
TP (ref.)	92	10,455.1	8.8 (7.2, 10.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S14A.SE Validation analysis: CRC as the outcome. Assessment of validity of CRC ascertainment: Hospital discharge diagnoses versus occurrence with CRC in the National Cancer Registry in Sweden[a]. Ascertainment assessment.
Not applicable for Denmark[a].

		Ascertainment source: Hospital discharge diagnoses[b]		
		Yes	**No**	**Total**
Ascertainment source: Cancer registry	**Yes**	28	<5	N.P.
	No	13	Not observed	Not estimable
	Total	41	Not estimable	Not estimable
Analysis based on summary over calendar years (Sweden only)[a]				
Ascertainment probability[c], (95% C.L.)		Estimated ascertainment probability		
		Swedish National Cancer Registry:	Swedish National Patient Register:	Both sources combined:
		N.P.	N.P.	N.P.

Abbreviations: C.I.: confidence interval; CRC: colorectal cancer; N.P.: not permissibl.
[a] In Denmark, cases of cancer are reported to the Danish Cancer Registry by direct link to hospital discharge diagnoses. Thus, the assumption of independent case ascertainment from the two sources involved is not fulfilled for a formal analysis of ascertainment probabilities in Denmark
[b] First occurrence of CRC as a primary or secondary discharge diagnosis
[c] Estimated by capture-recapture methodology

Table S14B.SE Validation analysis: CRC as the outcome. Assessment of validity of CRC ascertainment: CRC cases ascertained from Hospital discharge diagnoses (primary analysis) versus CRC cases ascertained from the National Cancer Registry only (sensitivity analysis) in Sweden. Association analyses.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: Colorectal cancer									
Therapy: GLM versus Other Anti-TNF (Table P1A.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
Other Anti-TNF (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P1B.SE)									
GLM (incl. overlap with Other Anti-TNF)	<5	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.	N.P.
TP (ref.)	N.P.	N.P.	N.P.	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; N.P.: not permissible; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S15A.SE Sensitivity analysis: Colectomy for intractable disease as the outcome. Excluding all-cause total colectomies where underlying primary discharge diagnosis is CRC. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.SE)									
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.5 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)
Other Anti-TNF (ref.)	158	6,094.3	25.9 (22.2, 30.3)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	21	545.7	38.5 (25.1, 59.0)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	4.6 (2.9, 7.4)	5.0 (3.0, 8.2)	4.3 (2.6, 7.1)
TP (ref.)	87	10,455.1	8.3 (6.7, 10.3)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S15B.SE Sensitivity analysis: Any colectomy as the outcome. Including any type (e.g. partial or total) of colectomy for any indication as the outcome. All point estimates are presented with 95% confidence interval.

	Number	Person-years (PY[a])	Incidence rate (per 1,000 PY)	Primary: IRR[b]			Sensitivity: IRR[b]		
				Crude	Adjusted, DAG[c]	Adjusted, FULL[c]	Crude	Adjusted, DAG[c]	Adjusted, FULL[c]
Outcome: All-cause TC									
Therapy: GLM versus Other Anti-TNF (Table P2A.SE)									
GLM (incl. overlap with Other Anti-TNF)	24	542.5	44.2 (29.7, 66.0)	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)	1.1 (0.7, 1.8)	1.5 (1.0, 2.2)	1.2 (0.8, 2.0)	1.2 (0.7, 1.9)
Other Anti-TNF (ref.)	183	6,071.6	30.1 (26.1, 34.8)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Therapy: GLM versus TP (Table P2B.SE)									
GLM (incl. overlap with Other Anti-TNF)	24	542.5	44.2 (29.7, 66.0)	4.4 (2.7, 7.0)	4.5 (2.7, 7.4)	3.9 (2.3, 6.4)	4.5 (2.9, 7.1)	4.8 (3.0, 7.6)	4.1 (2.5, 6.5)
TP (ref.)	102	10,431.2	9.8 (8.1, 11.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: CRC: colorectal cancer; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] Person-years calculated as outlined in Section 9.8.2 and SAP, Section 6.3.4

[b] IRR: Incidence Rate Ratio

[c] For covariates included: See tables listed referred to in the specification of therapy comparison

Table S16.SE Sensitivity analysis: All-cause TC as the outcome. Cases, PYs and crude incidence rates of all-cause TC within and outside 90-day risk window.

Outcome: All-cause TC	Therapy cohort[a]		
	GLM (incl. overlap with Other Anti-TNF) (N=298)	Other Anti-TNF (N=3,385)	TP (N=5,146)
Within 90-day risk window			
n[b]	22	170	156
Person-years, PY[c]	783.1	7,363.8	12,534.0
Crude Incidence rate per 1,000 PY	28.1	23.1	12.4
95% Confidence Interval	18.5, 42.7	19.9, 26.8	10.6, 14.6
Outside of 90-day risk window			
n[d]	19	128	107
Person-years, PY[d]	606.6	4,571.9	6,493.2
Crude Incidence rate per 1,000 PY	31.3	28.0	16.5
95% Confidence Interval	20.0, 49.1	23.5, 33.3	13.6, 19.9
All follow-up time			
n[e]	41	298	263
Person-years, PY[e]	1,389.7	11,935.7	19,027.1
Crude Incidence rate per 1,000 PY	29.5	25.0	13.8
95% Confidence Interval	21.7, 40.1	22.3, 28.0	12.2, 15.6

Abbreviations: GLM: golimumab; PY: person years; TC: total colectomy; TNF: tumor necrosis factor alpha; TP: thiopurine

[a] For patients entering more than one therapy cohort outcomes are counted for each of these therapy cohorts (i.e. therapy cohort entries are not mutually exclusive). The sum of outcomes across therapy cohorts may be higher than the number of outcomes occurring in the unique patient.

[b] Number of patients with first outcome registered within 90-day risk windows

[c] Person-years calculated using 90-day risk window as outlined in Section 9.8.2 and SAP, Section 6.3.4 and Figure 3

[d] Number of patients and person-years were outside of 90-day risk window

[e] Number of patients and person-years were calculated using all follow-up time

Table S17.SE Sensitivity analysis: All-cause TC as the outcome. Assessing the effect modification by time period concerning switch from one therapy to the next. All point estimates are presented with 95% confidence interval.

Outcome: All-cause TC		**Colectomy within 90 days**		
Therapy: GLM versus Other Anti-TNF		**Yes**	**No**	**Total**
Short time: Switch where Drug B starts as an overlapping drug	*Drug B: GLM*	<5	81	N.P.
	Drug B: Other Anti-TNF	0	18	18
Longer time: Switch where Drug B does not start as an overlapping drug	*Drug B: GLM*	0	37	37
	Drug B: Other Anti-TNF	0	16	16

Abbreviations: GLM: golimumab; N.P.: not permissible; TC: total colectomy; TNF: tumor necrosis factor alpha

Table S18A.SE Sensitivity analysis: Quantitative Bias Analysis (QBA); Sweden only.

Bias parameter	Value	External source
Prevalence of prior IFX use in GLM cohort, P_{c1}	Median (min, max): 0.386 (0.291, 0.491)	IQVIA validation study (see Annex 3)
Prevalence of prior IFX use in ADA cohort, P_{c0}	Median (min, max): 0.314 (0.273, 0.358)	IQVIA validation study (see Annex 3)
Hazard ratio comparing IFX vs. no IFX exposure, i.e., association between prior IFX exposure and colectomy outcome, HR_{cd}	Point estimate (95% CI): 7.2 (1.0, 64.5)	Studies by Taxonera et al (ref. 9 and 10)

Abbreviations: ADA: adalimumab; GLM: golimumab; IFX: infliximab; QBA: quantitative bias analysis

Table S18B.SE Sensitivity analysis: Quantitative Bias Analysis (QBA); Sweden only. Adjusting for unmeasured confounder of prior IFX exposure for outcome of all-cause TC (GLM vs ADA cohort).

				Main study			QBA		
Outcome: All-cause TC	**Number N**	**Person-years (PY[a])**	**Incidence rate (per 1,000 PY)**	**IRR Crude (95% CI)[b]**	**IRR Adjusted, DAG (95% CI)[b]**	**IRR Adjusted, FULL (95% CI)[b]**	**IRR Crude (95% CI)[c]**	**IRR Adjusted, DAG (95% CI)[c]**	**IRR Adjusted, FULL (95% CI)[c]**
Therapy: GLM versus ADA									
GLM (incl. overlap with ADA)	21	548.9	38.3 (24.9, 58.7)	1.6 (1.0, 2.5)	1.5 (0.9, 2.4)	1.4 (0.9, 2.2)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.0 (0.8, 1.3)
ADA (ref.)	129	5,260.7	24.5 (20.6, 29.1)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)

Abbreviations: ADA: adalimumab; CI: confidence interval; DAG: directed acyclic diagrams; GLM: golimumab; IRR: incidence rate ratio; PY: person years; QBA: quantitative bias analysis; TC: total colectomy

[a] Person-years calculated as outlined in Section 9.8.2 (however ignoring IFX as an exposure) and SAP, Section 6.3.4

[b] IRR_{obs}: Observed Incidence Rate Ratio. Obtained from Sweden by rerunning the analysis for the outcome of all-cause TC comparing the GLM cohort and ADA cohort using the Poisson regression analysis (ignoring IFX as a confounder variable), adjusting for multiple potential cofounders available (see Table P2A.SE) in the main study using the automated database; the variables of extent of UC and history of prior biologic therapy were excluded (see text)

[c] IRR: QBA adjusted IRR and 95% simulation interval using the Lash (2010) method of probabilistic bias analysis

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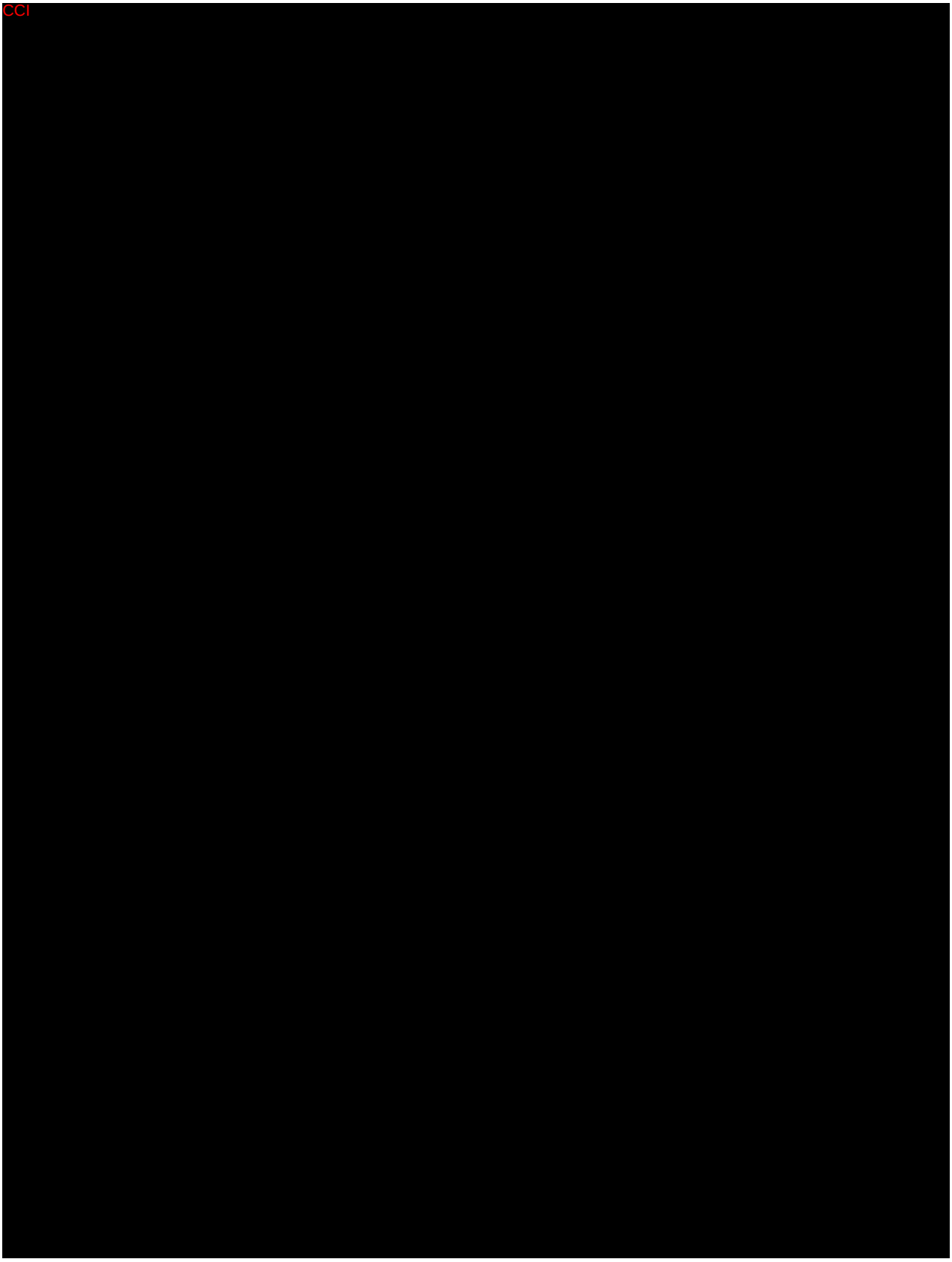

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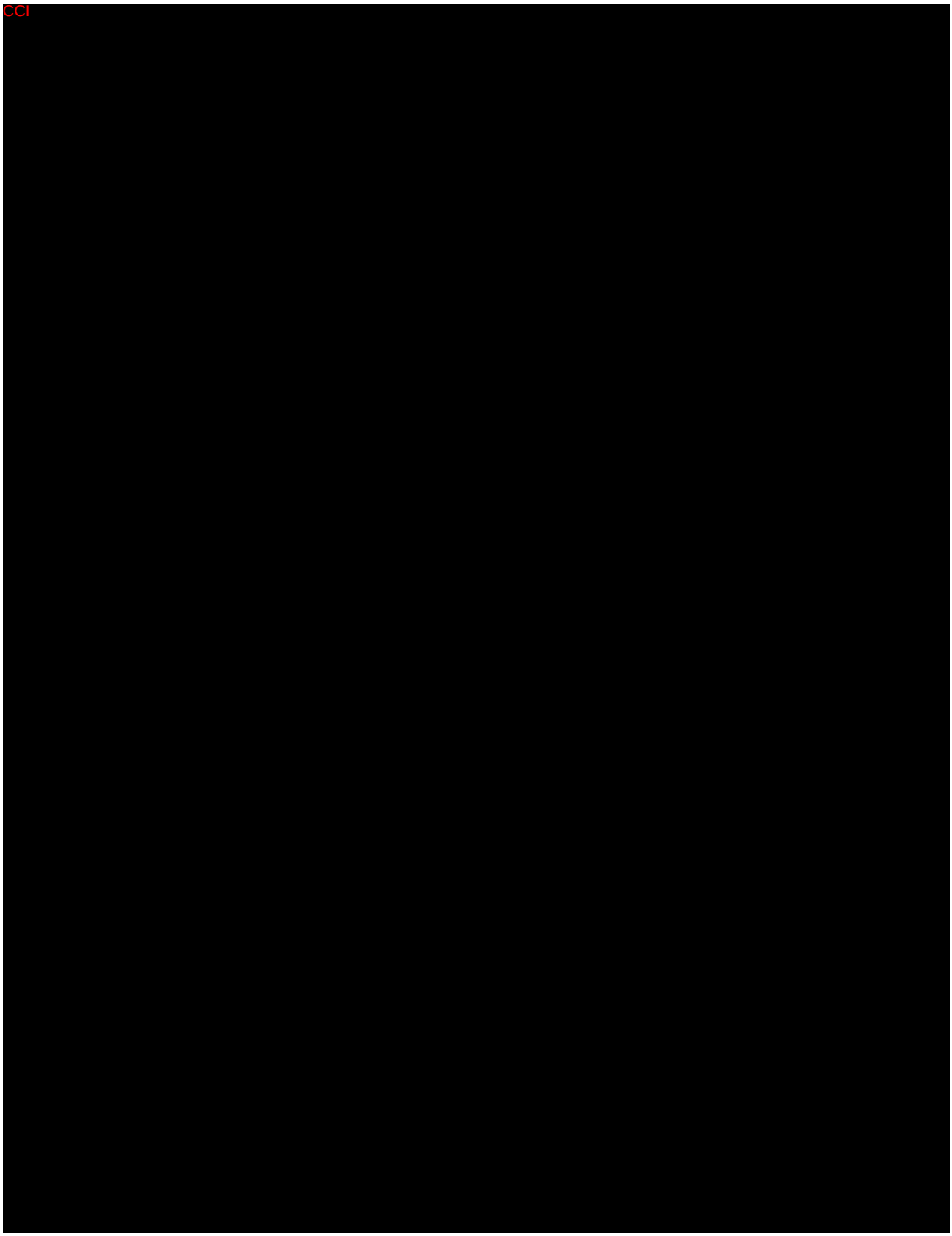

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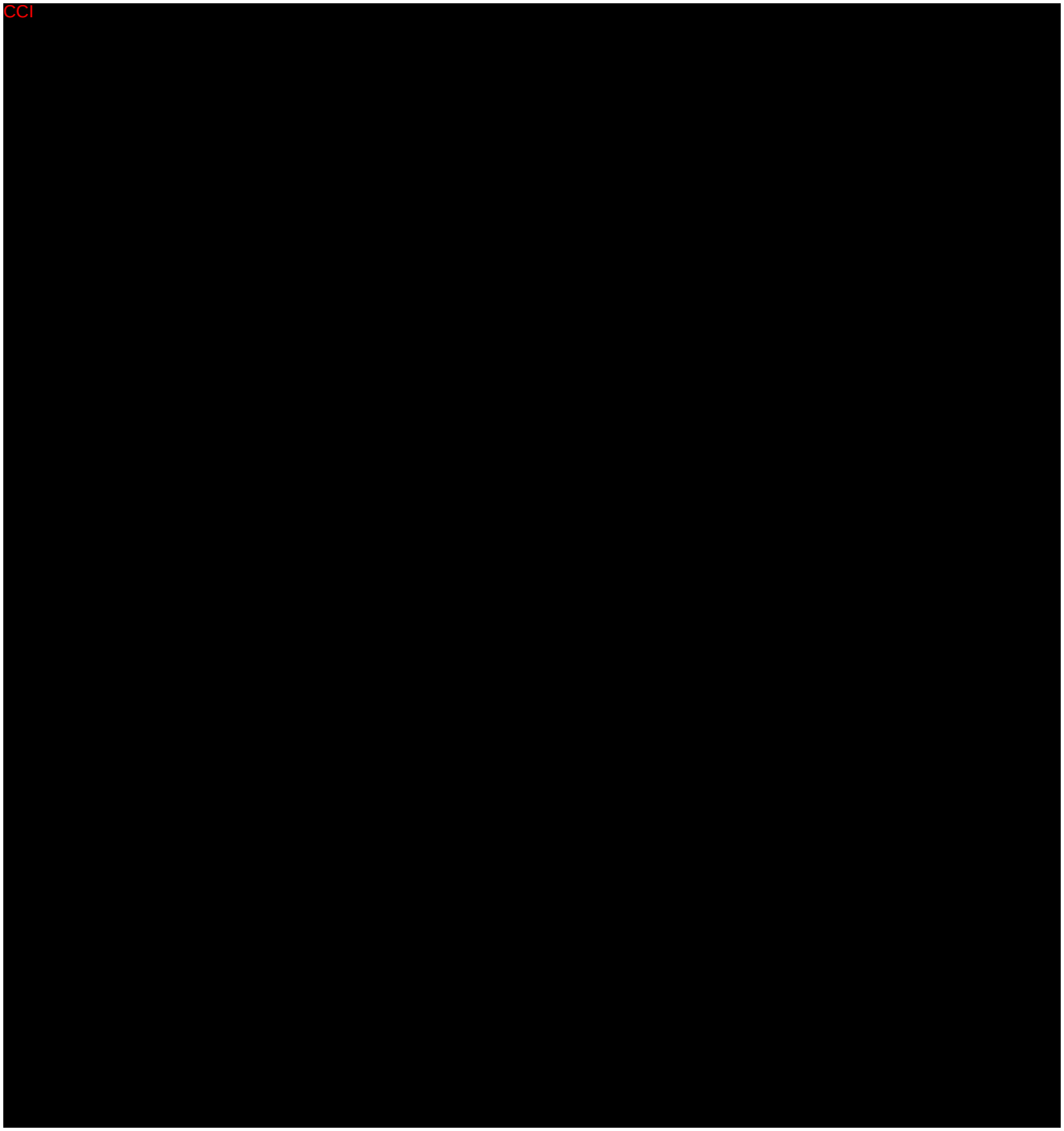

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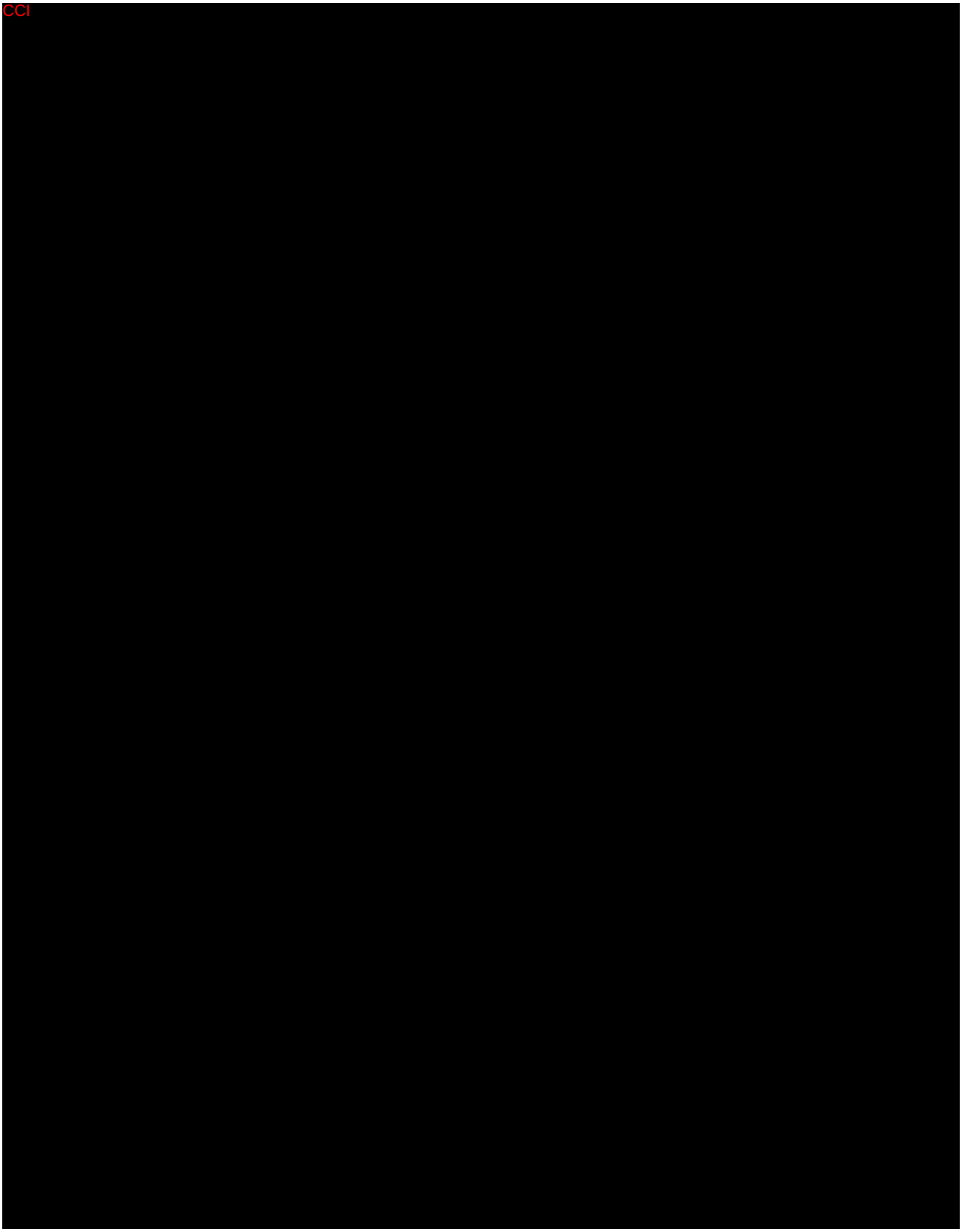

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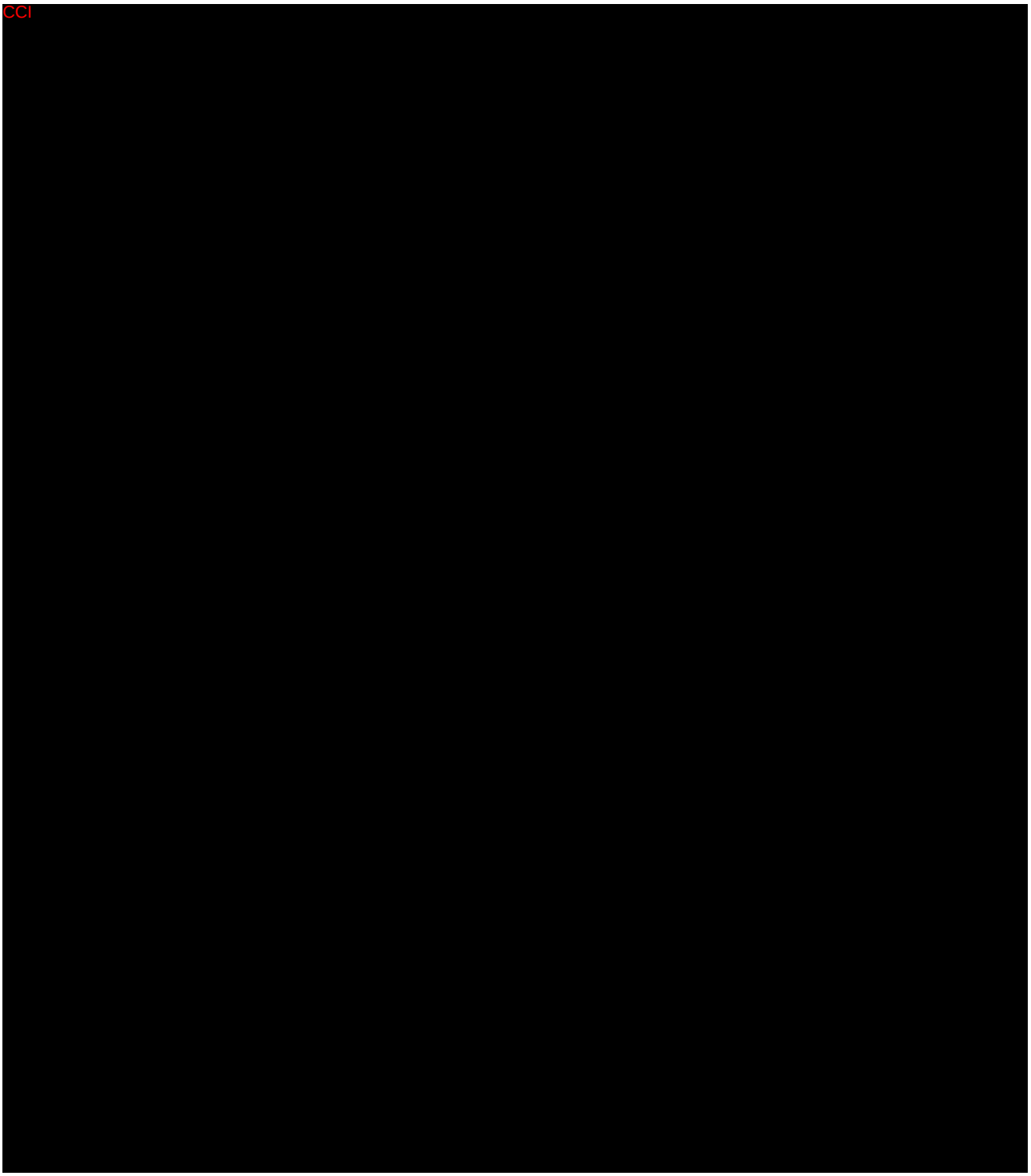

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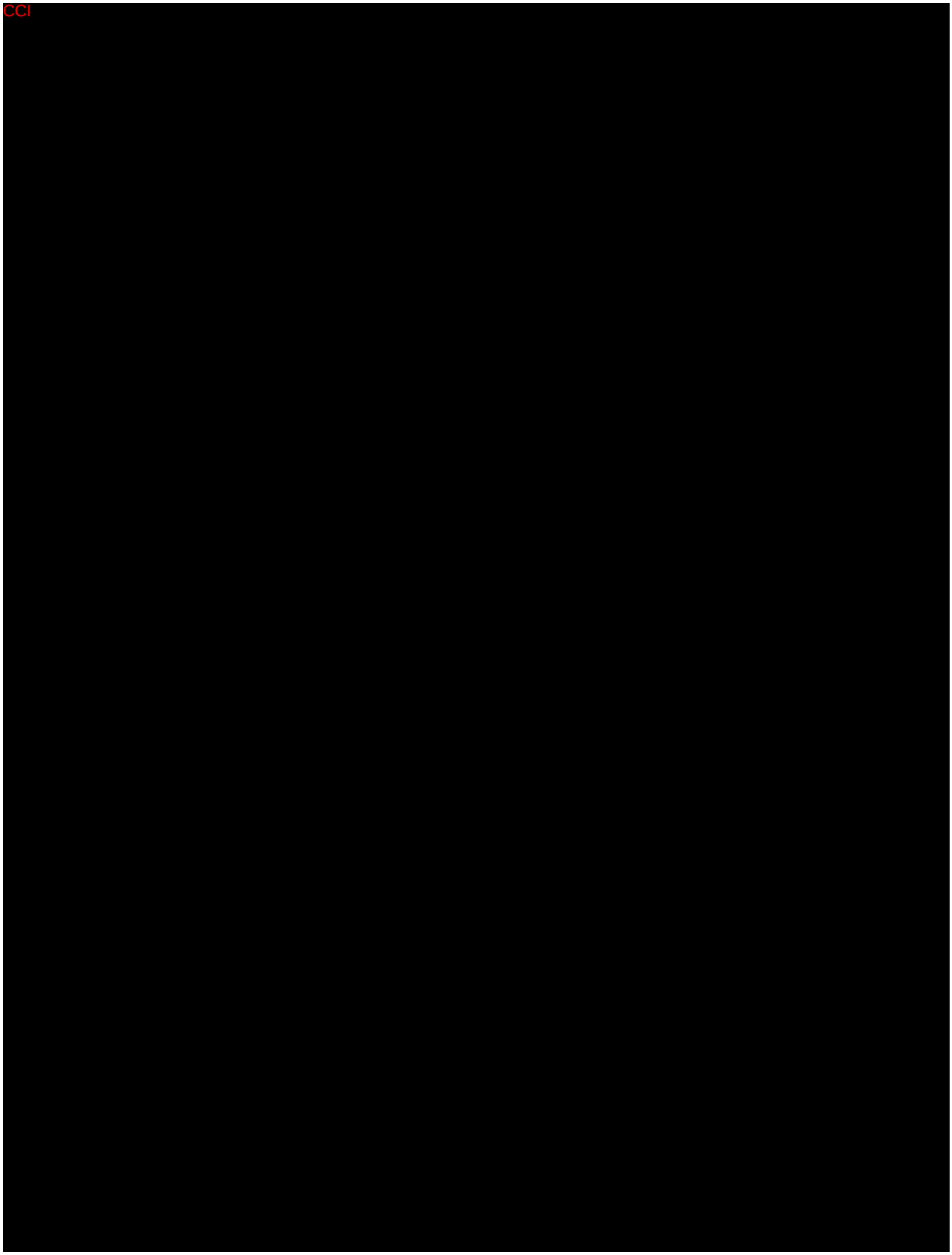

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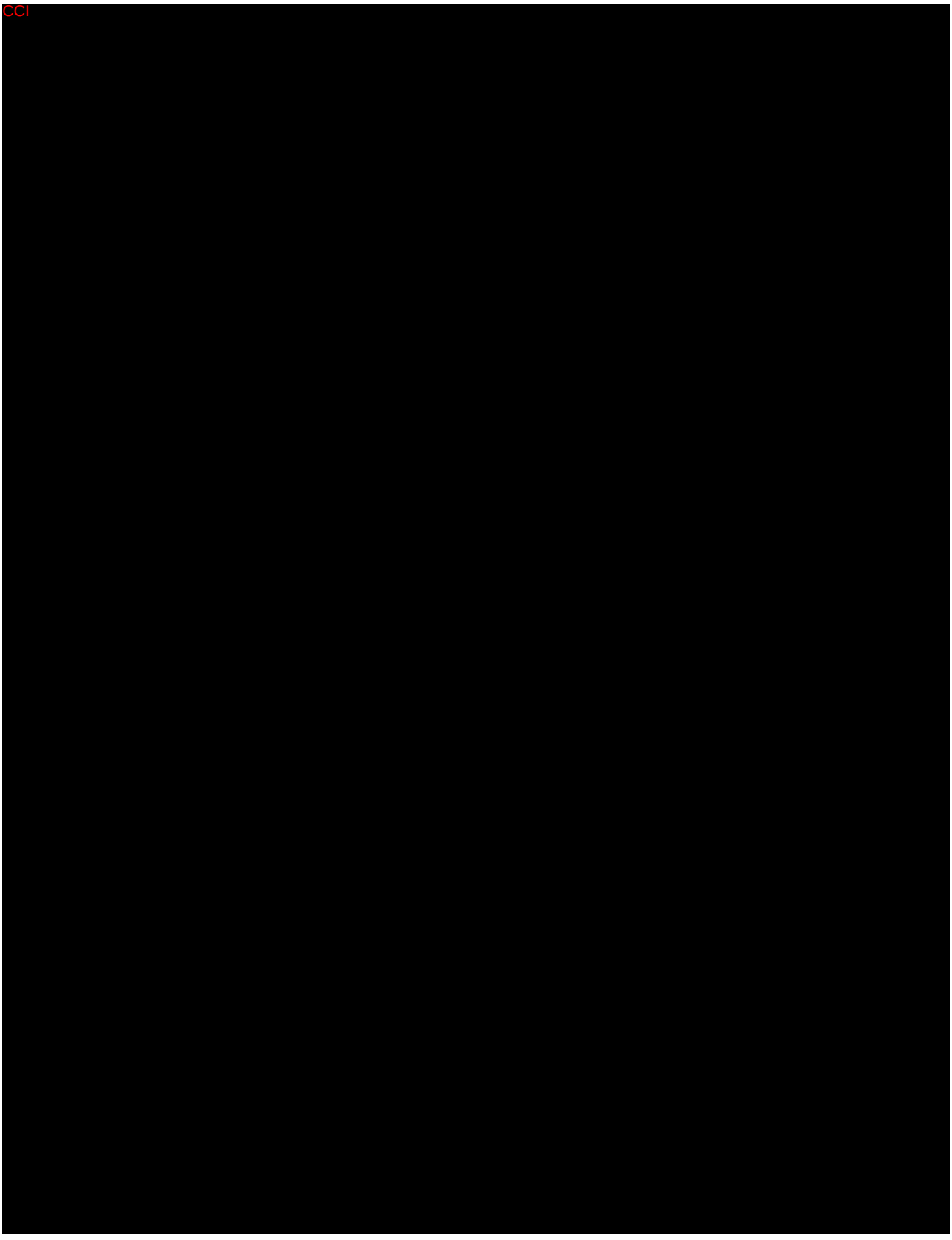

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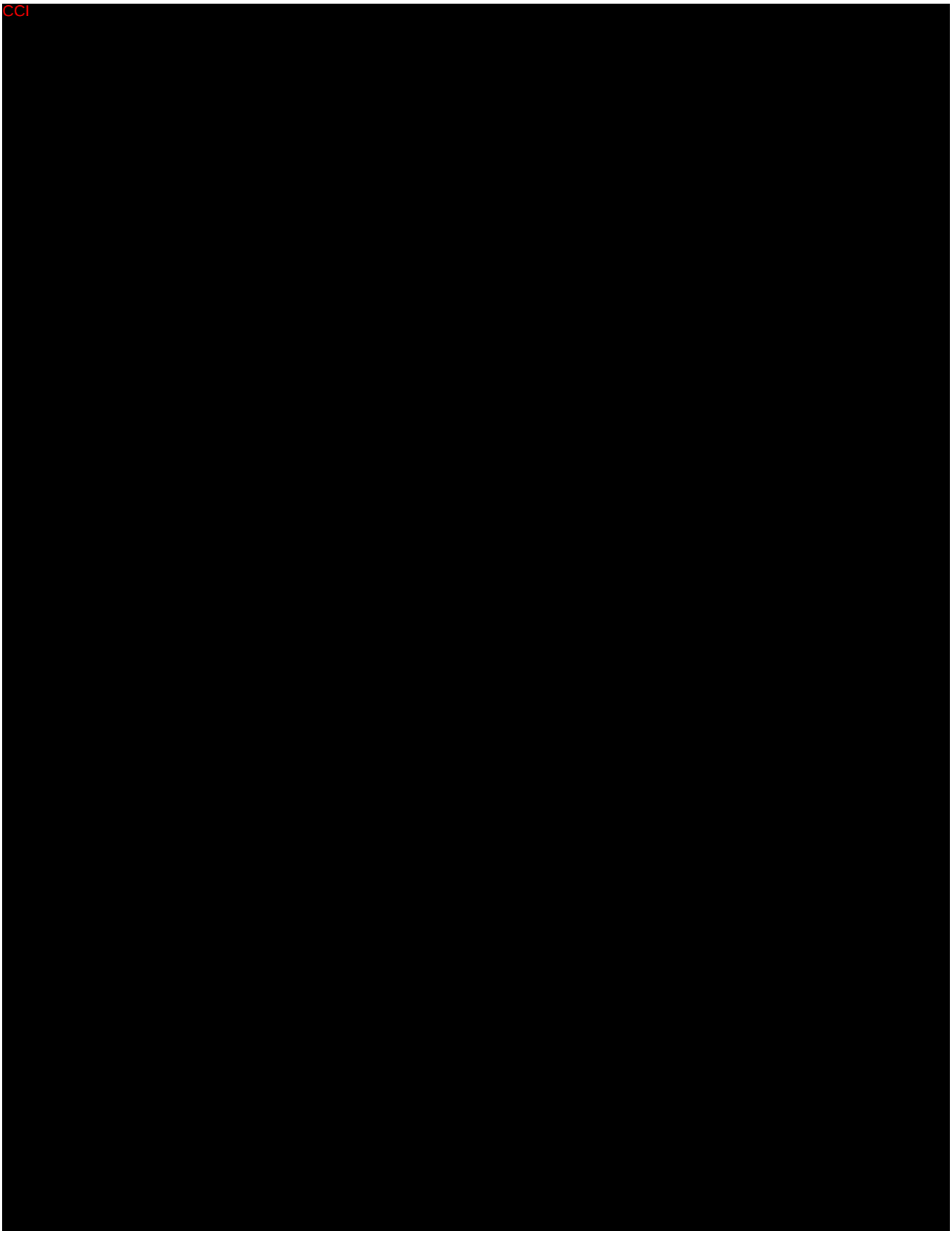

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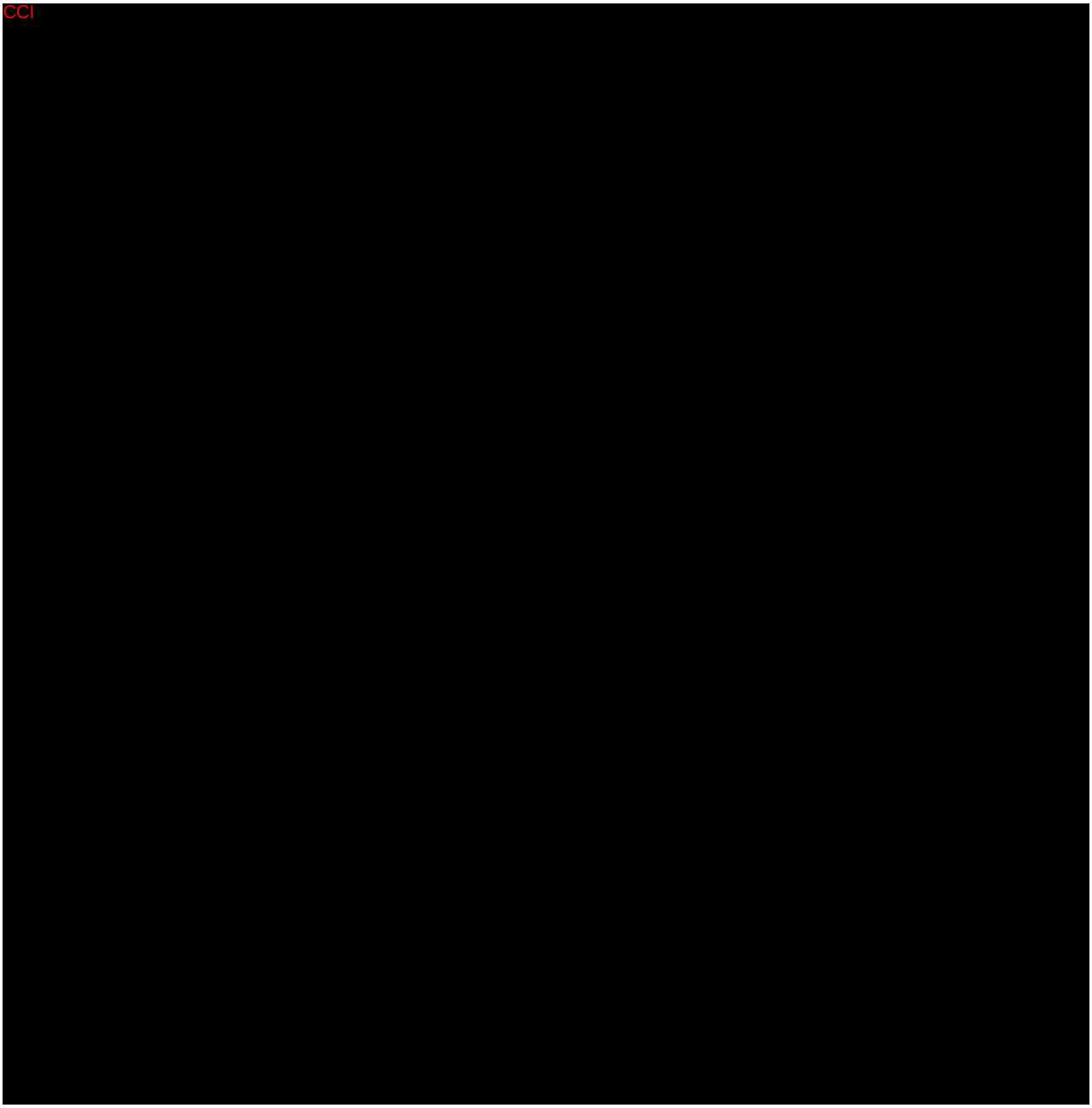

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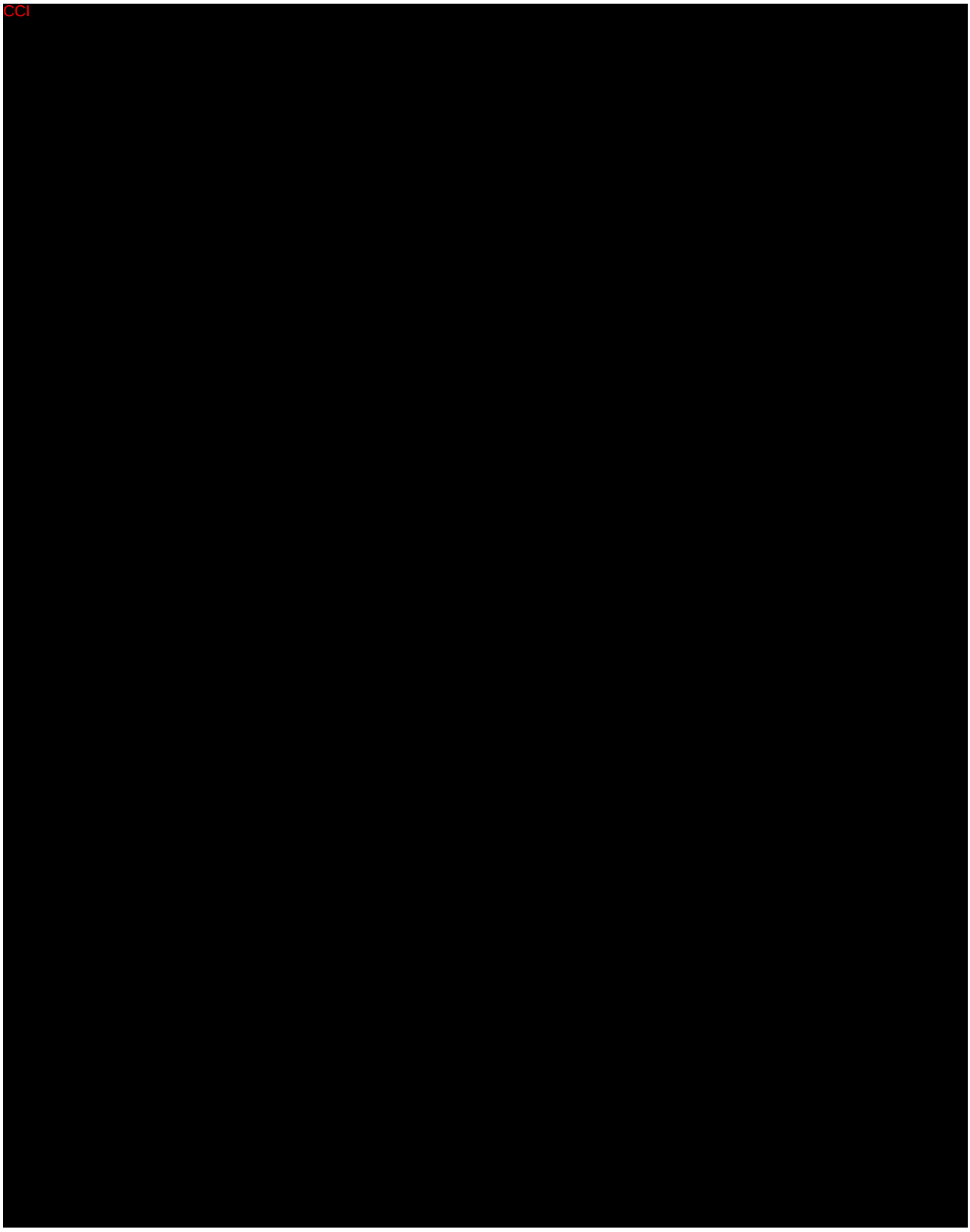

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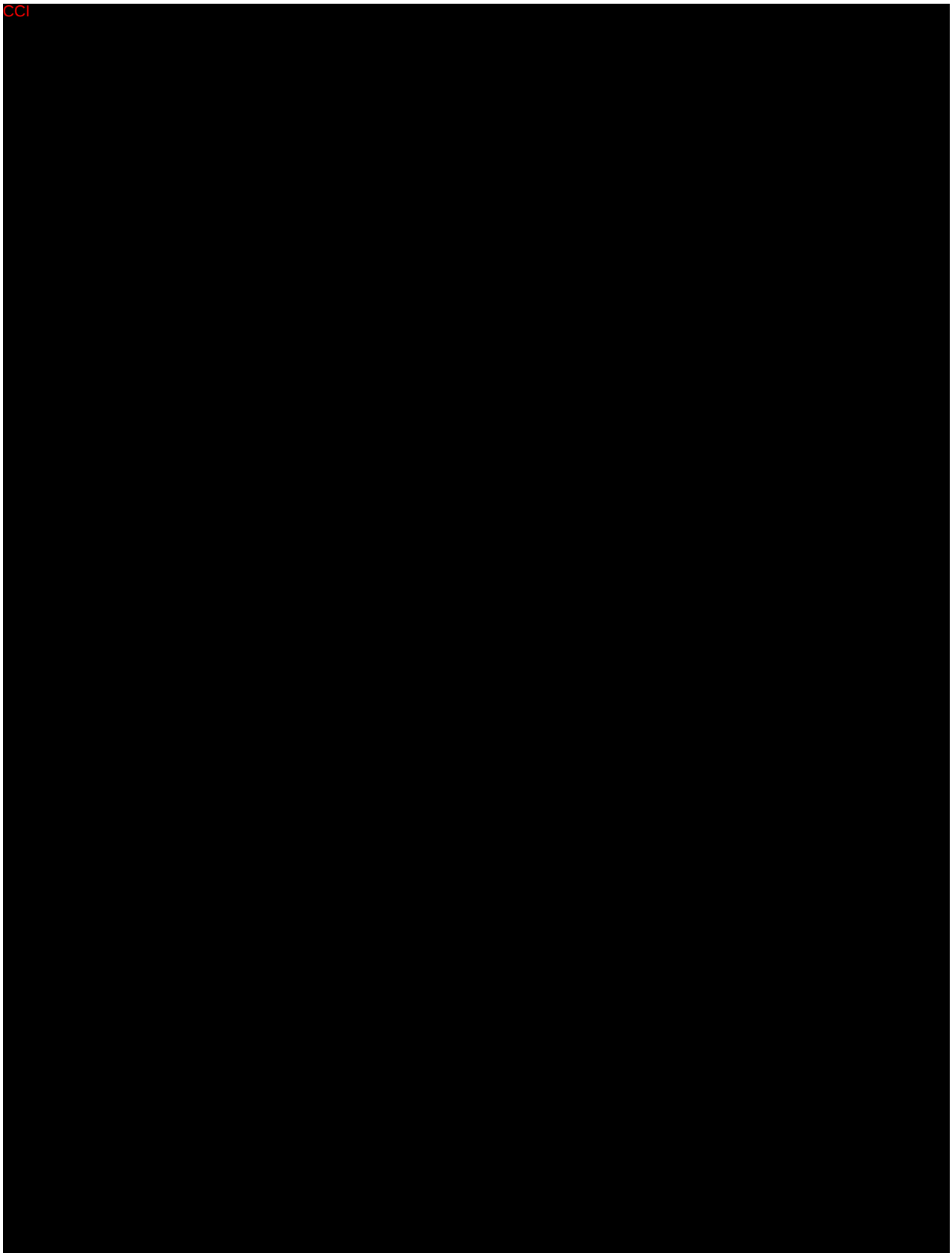

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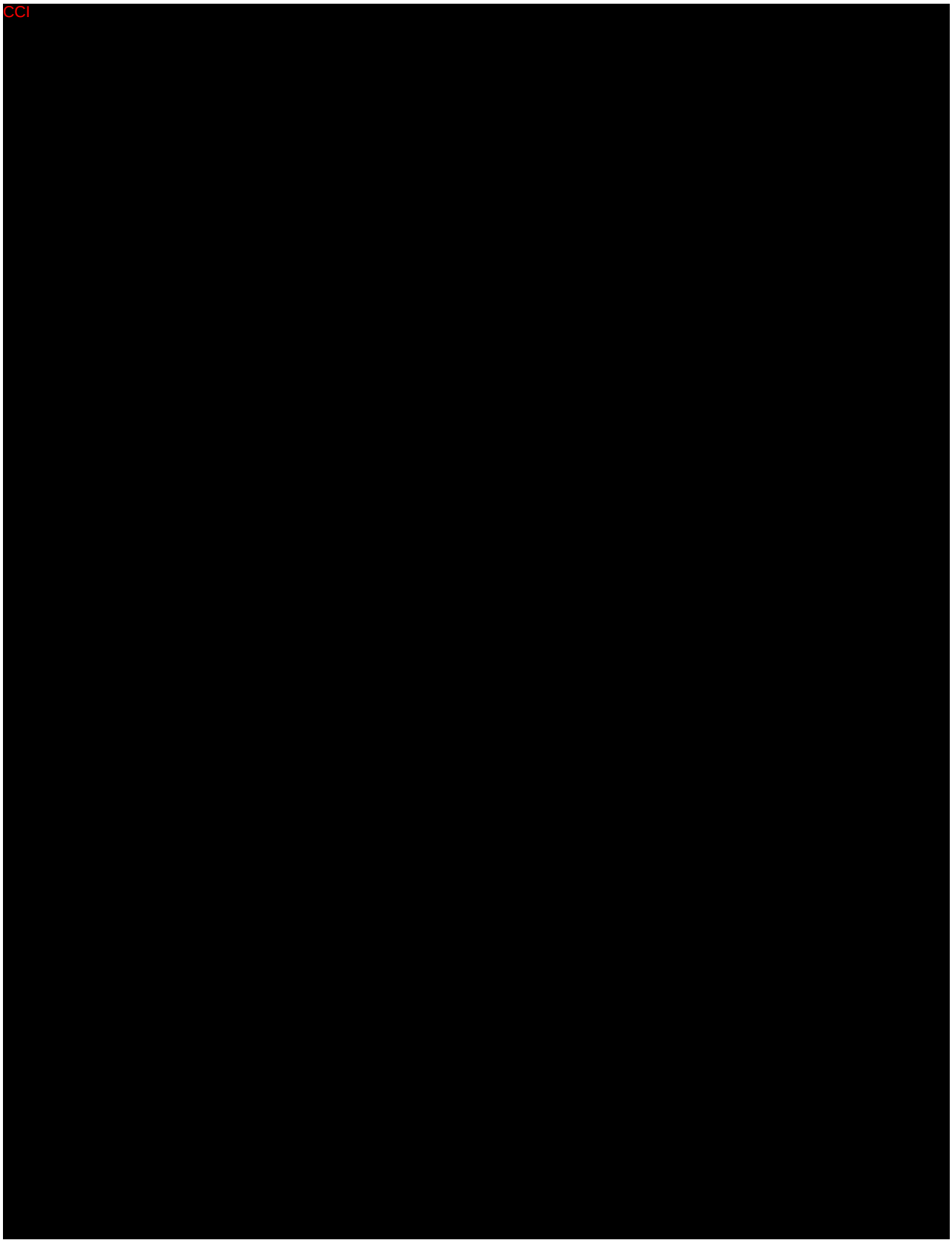

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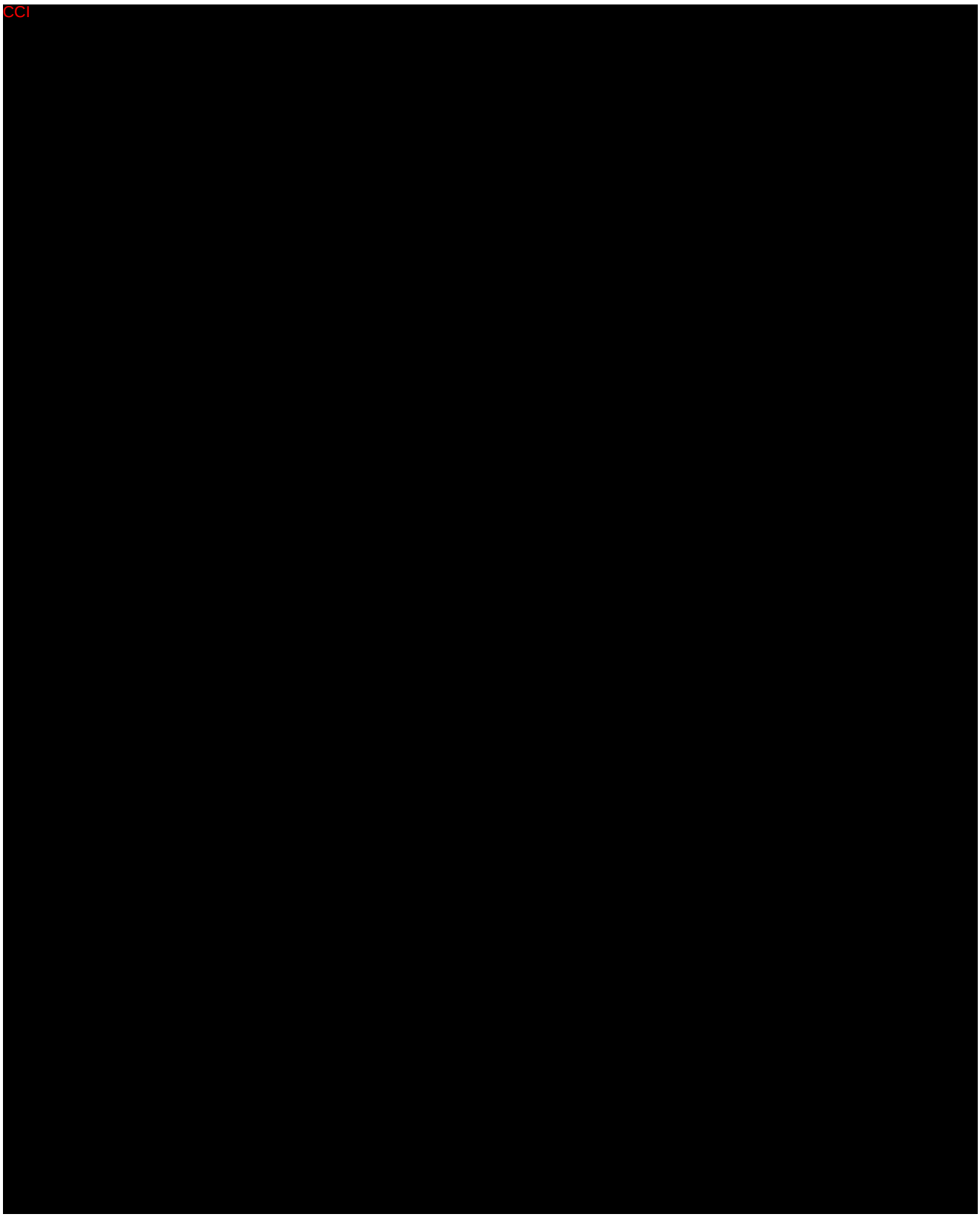

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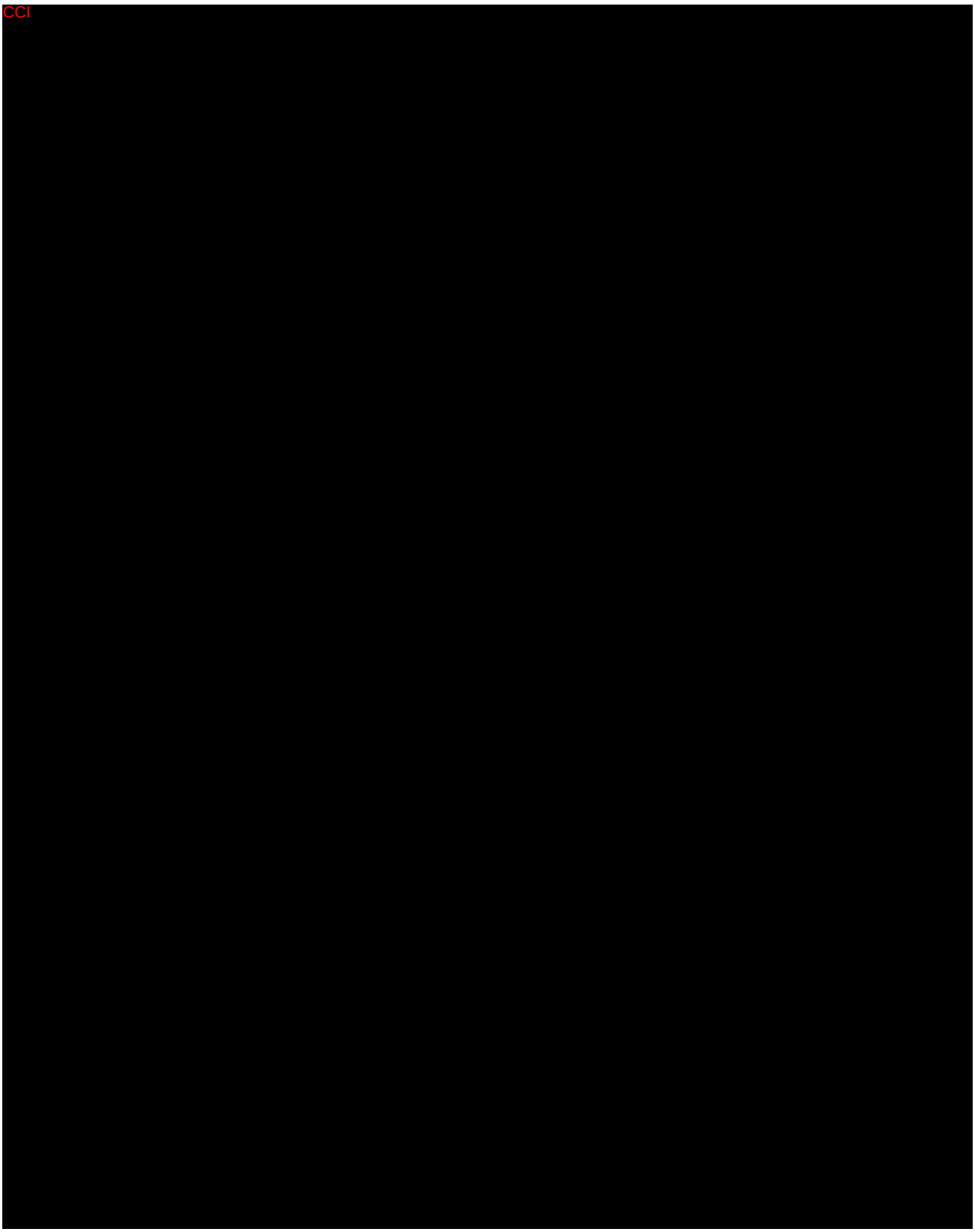

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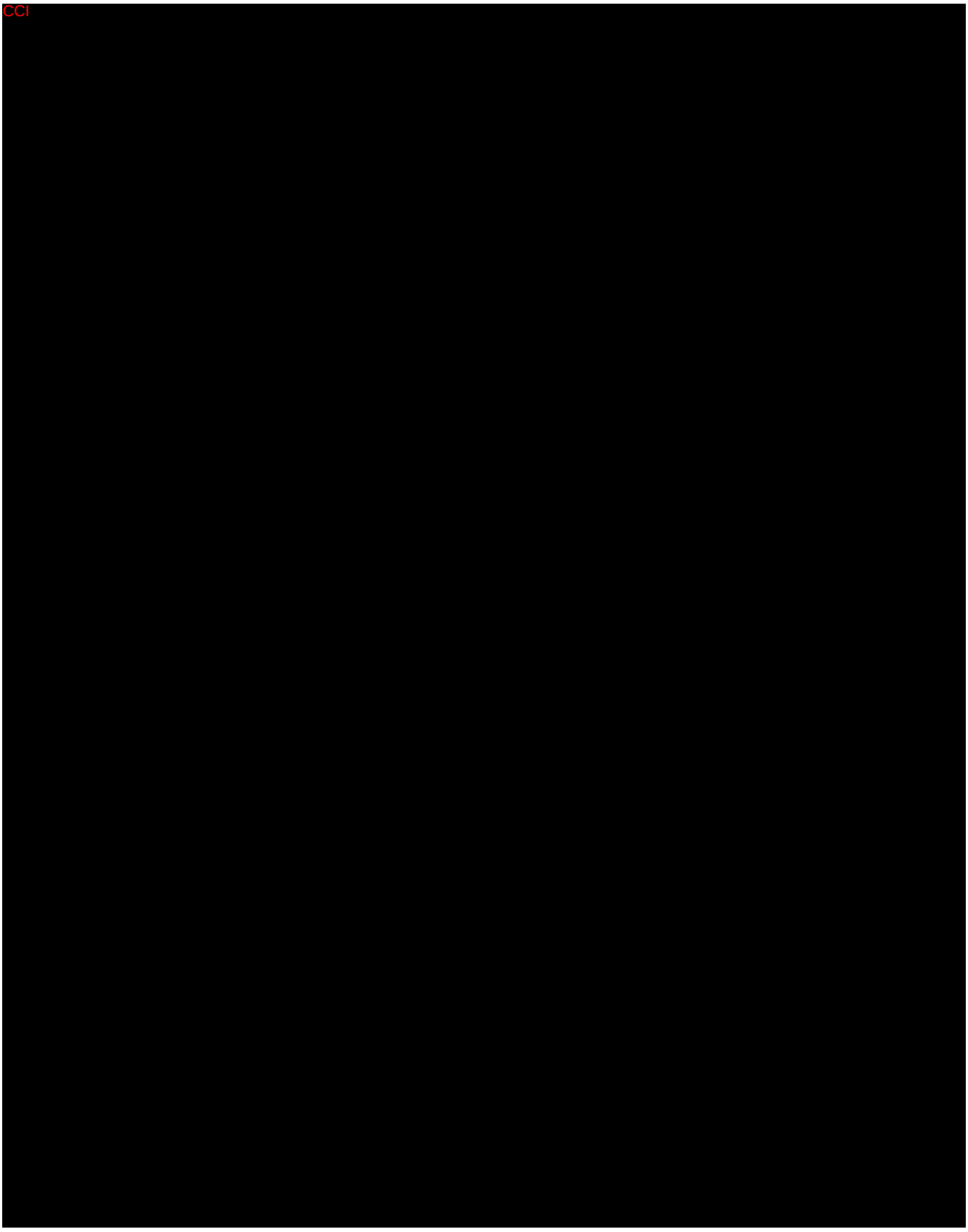

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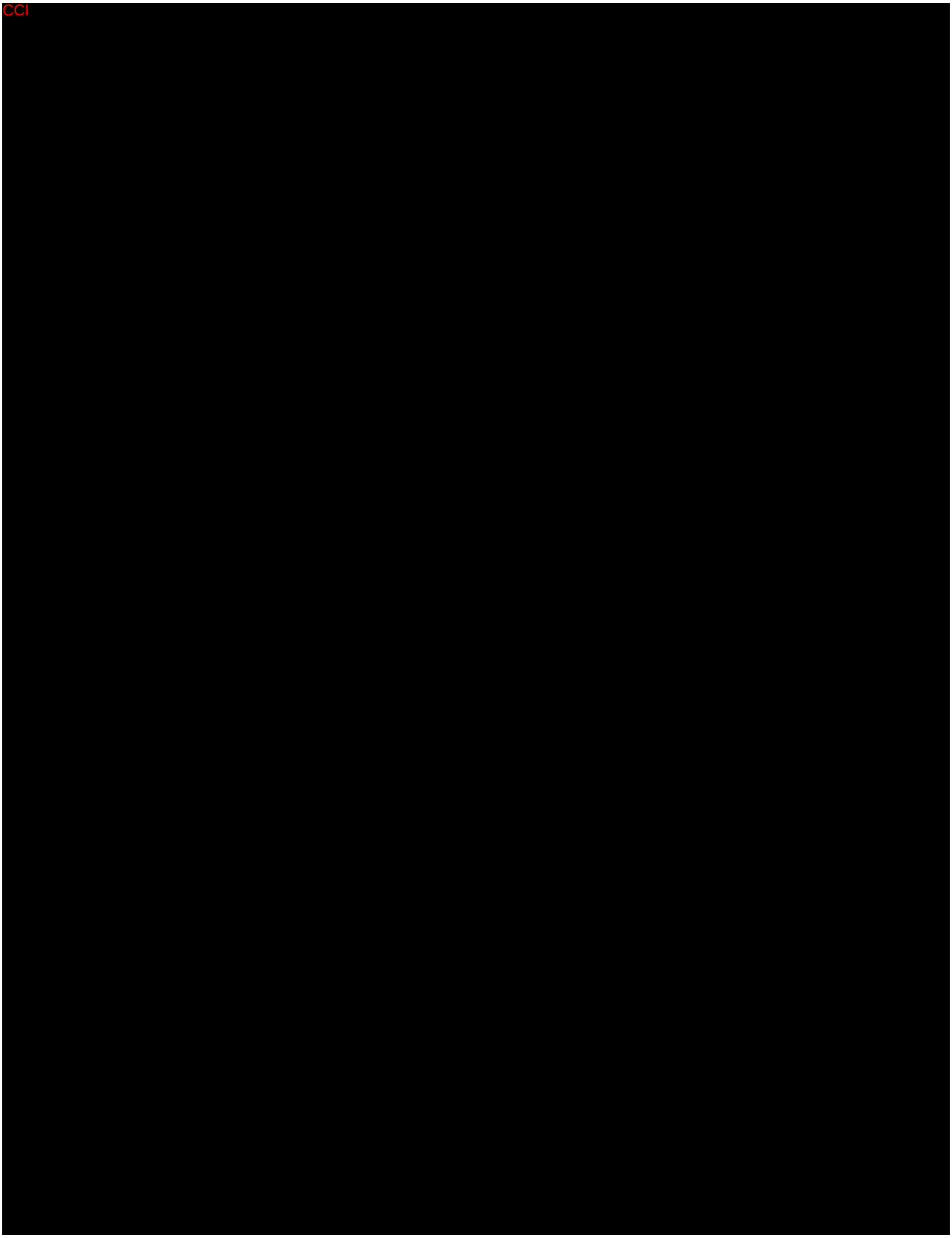

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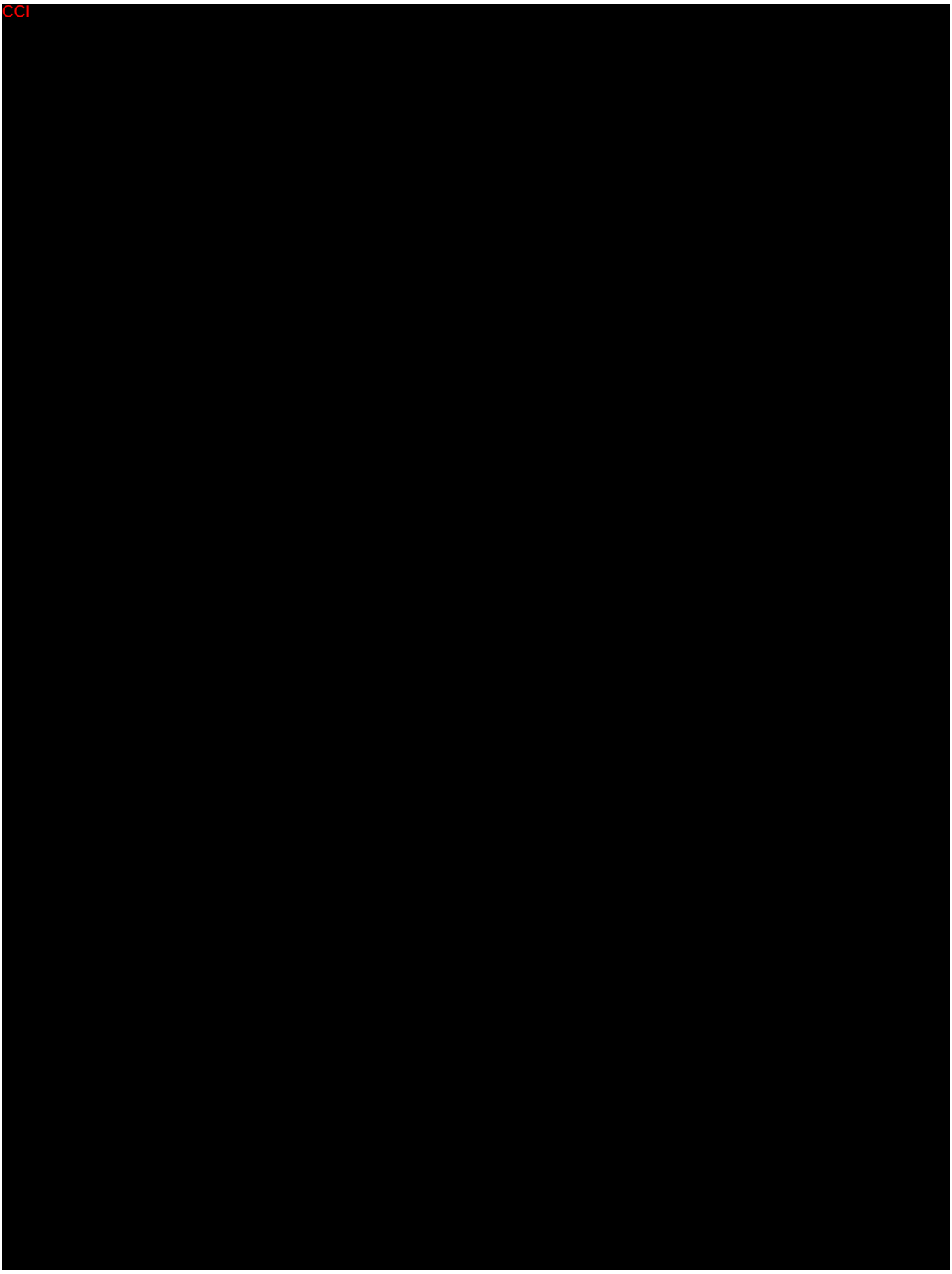

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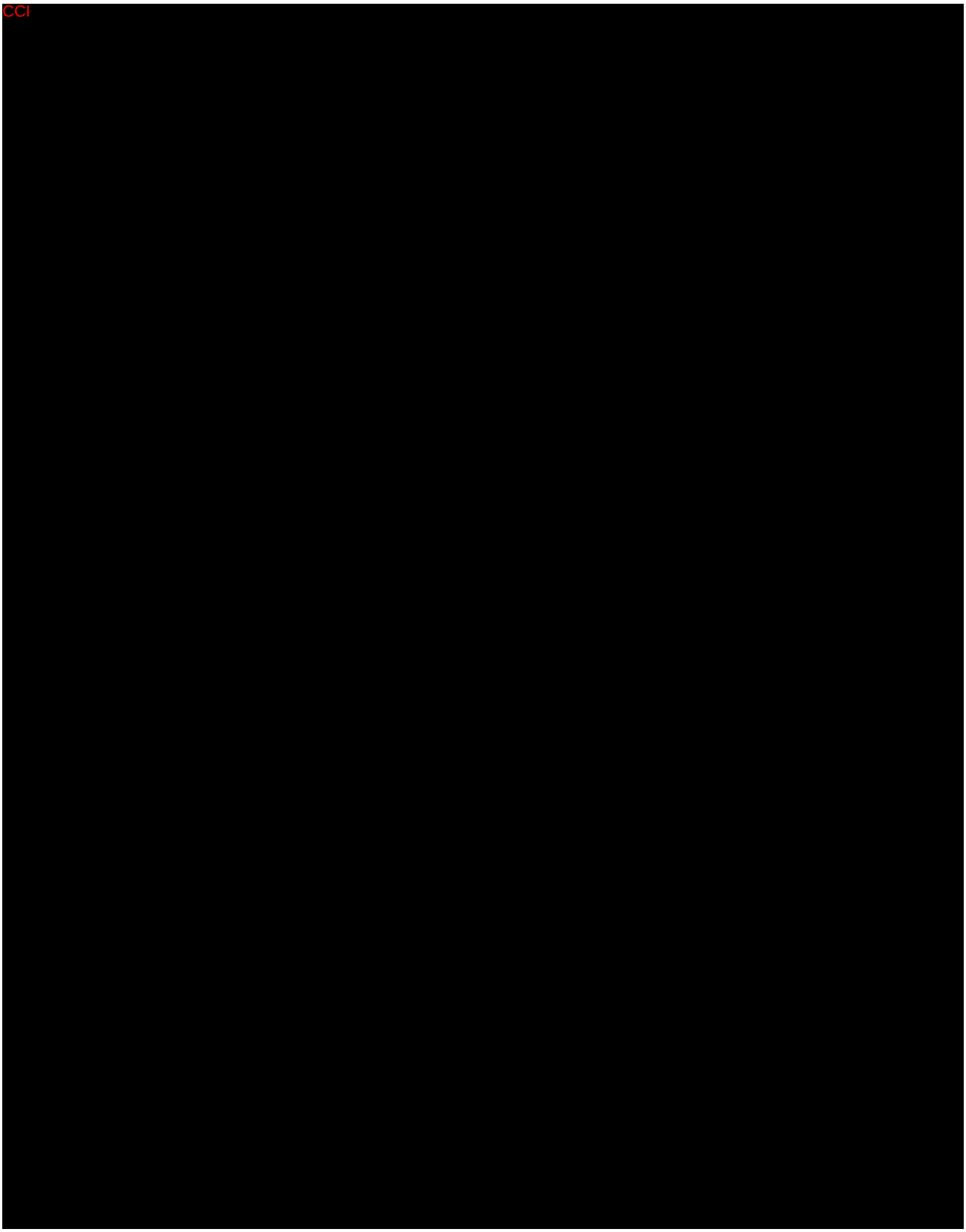

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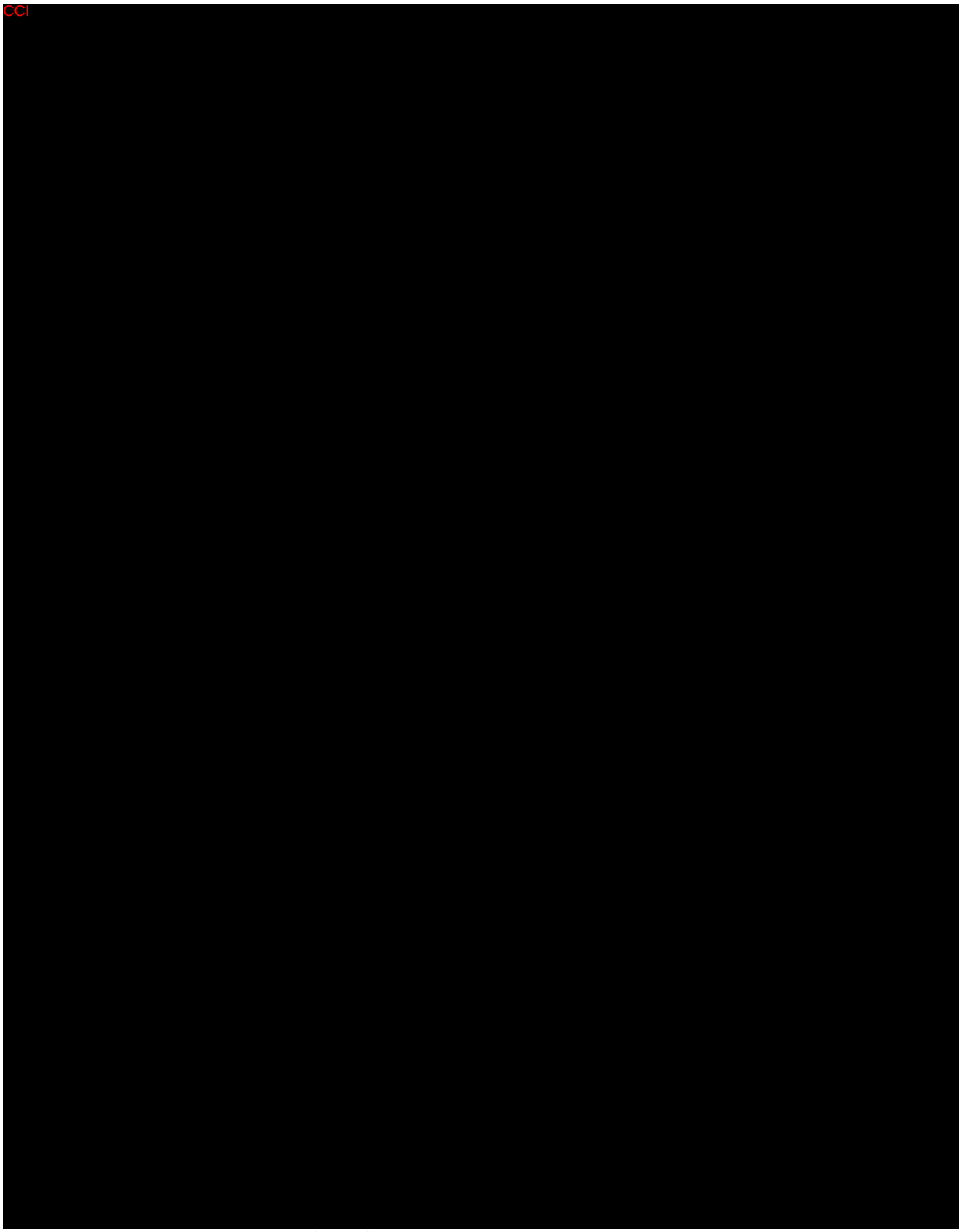

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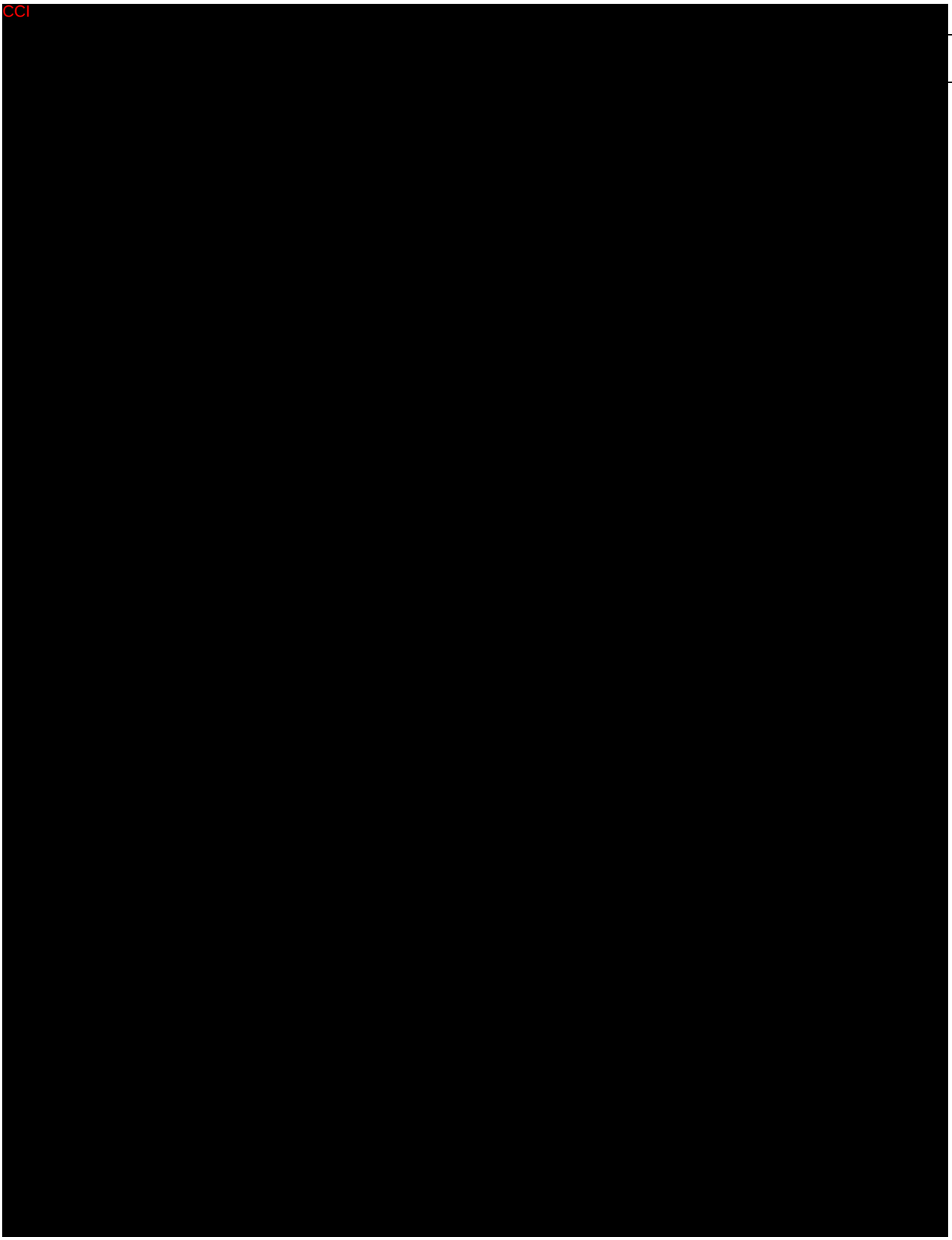

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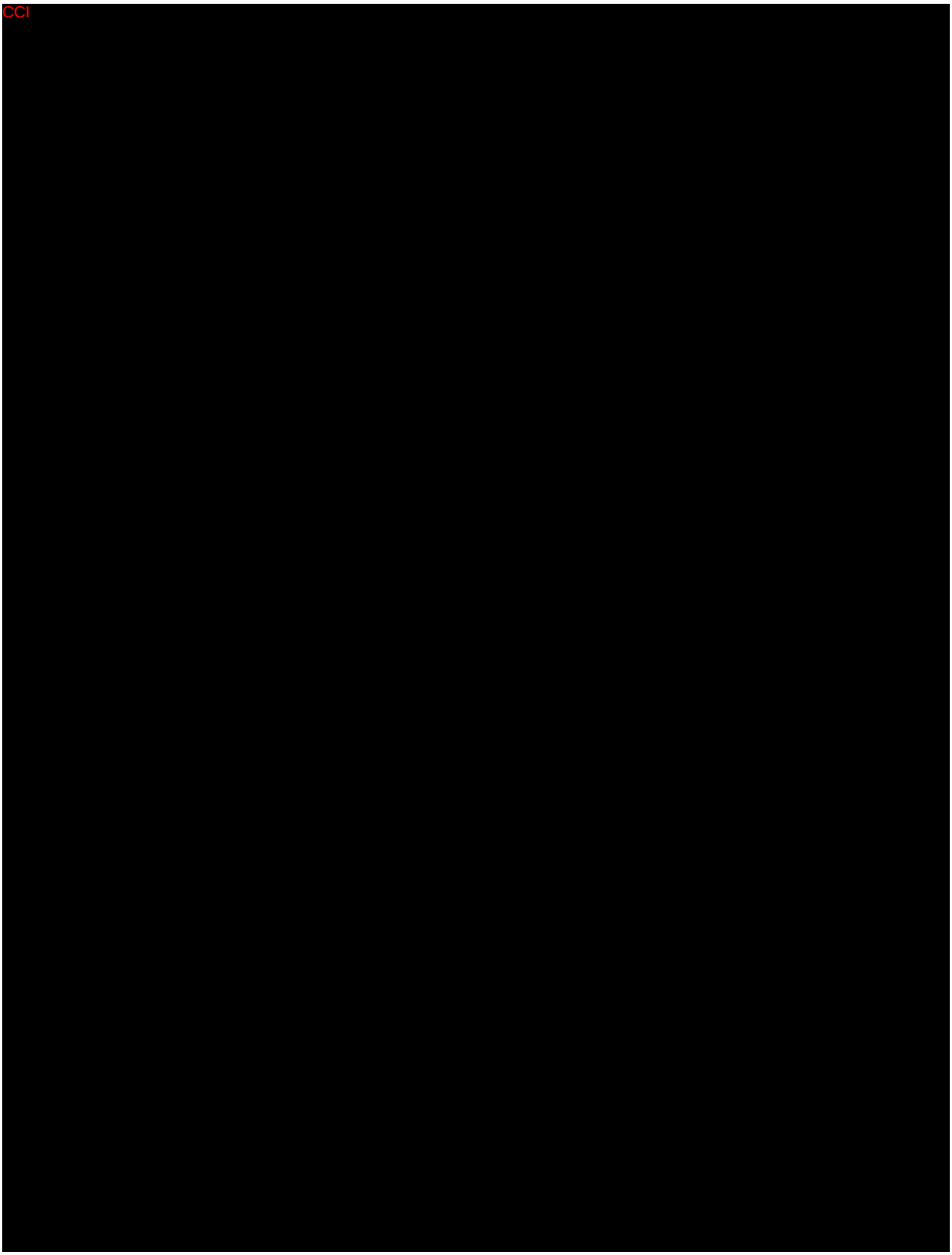

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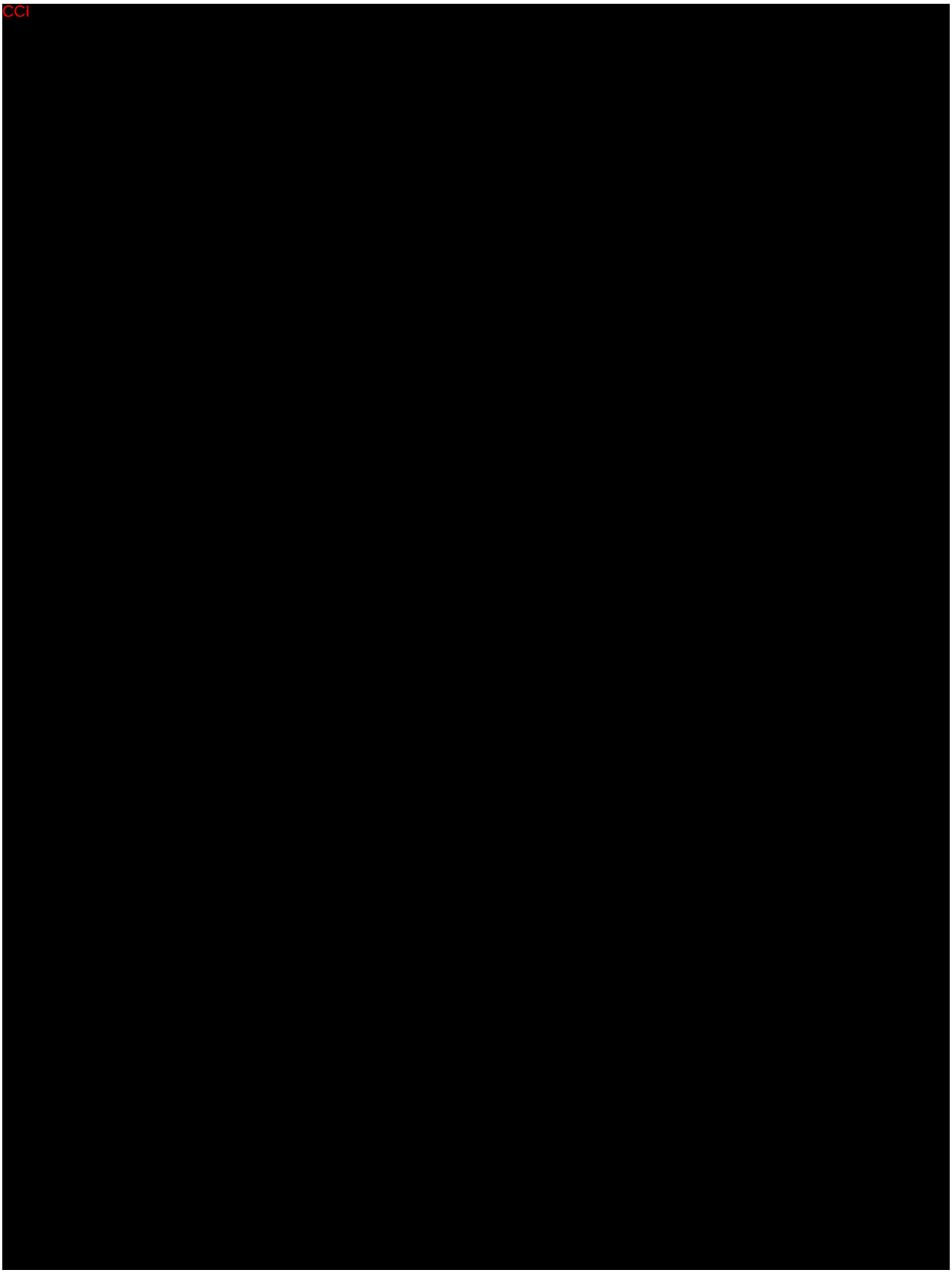

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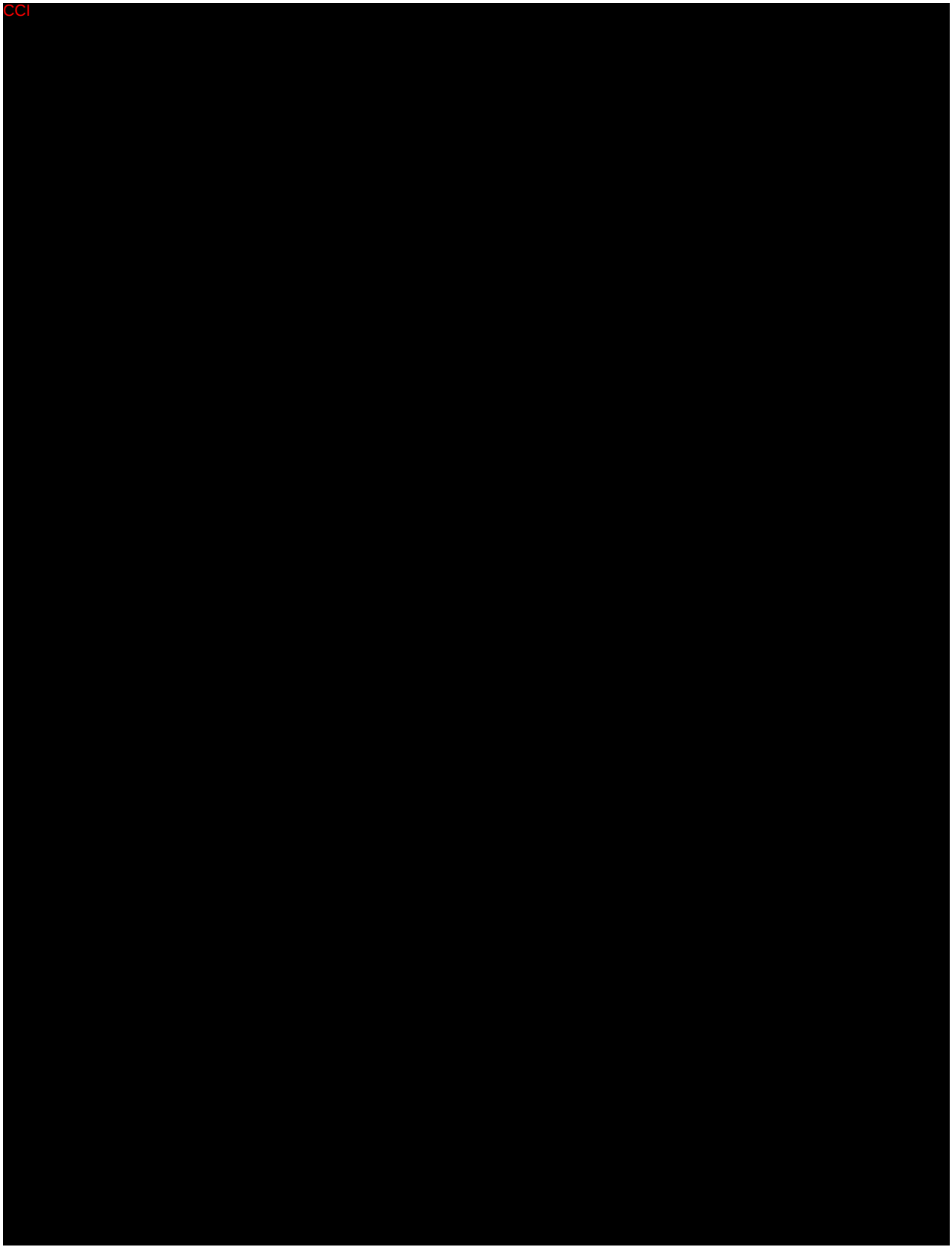

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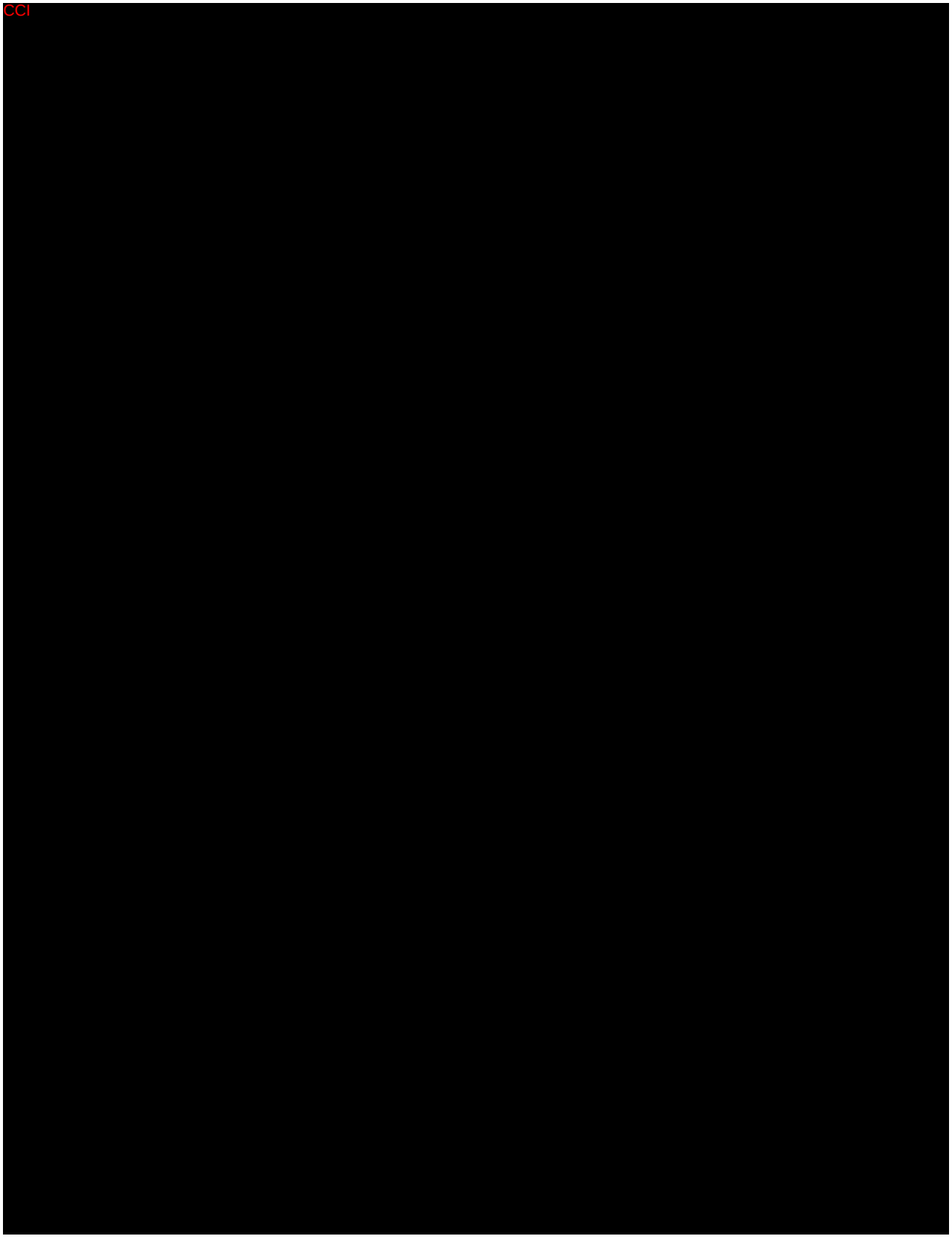

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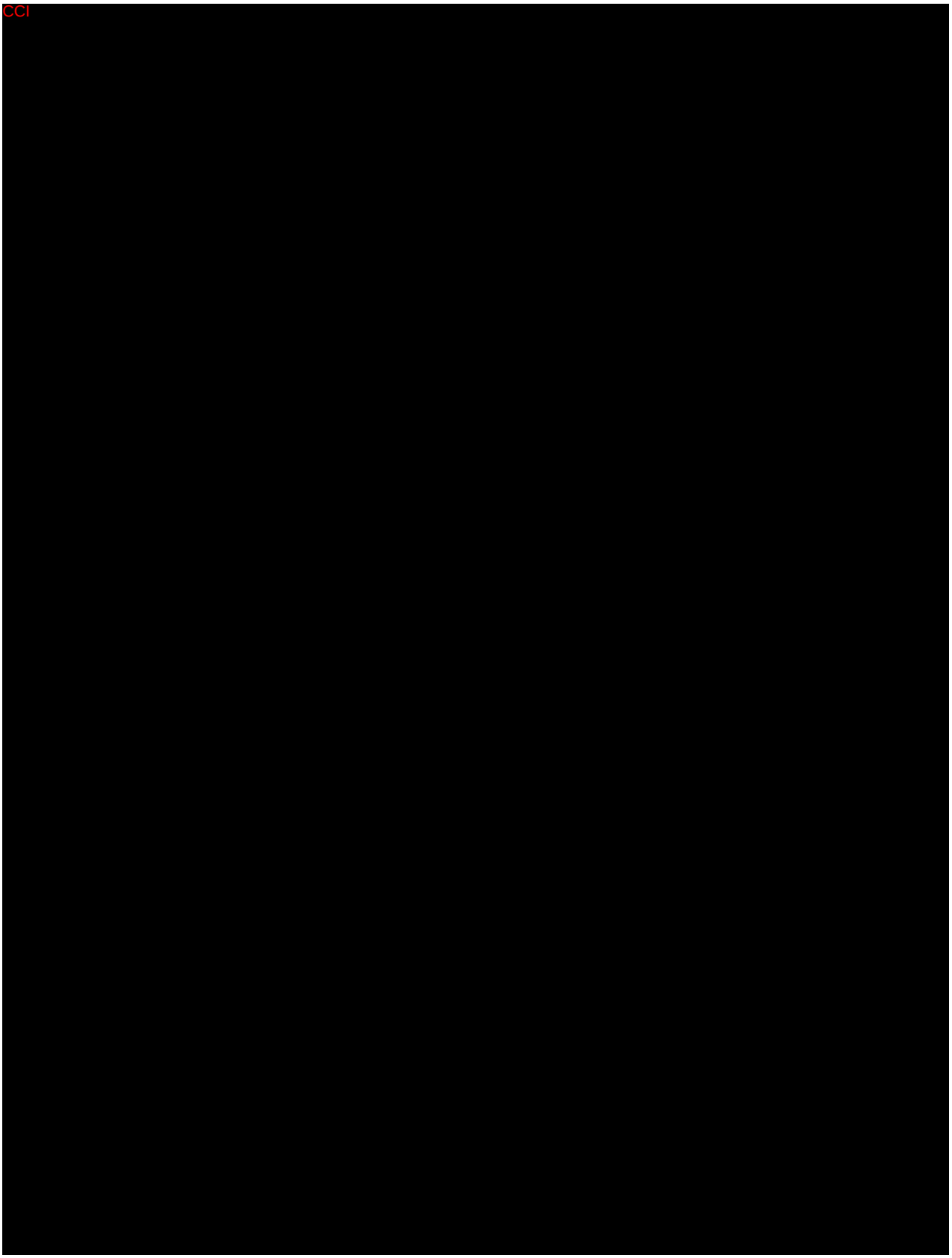

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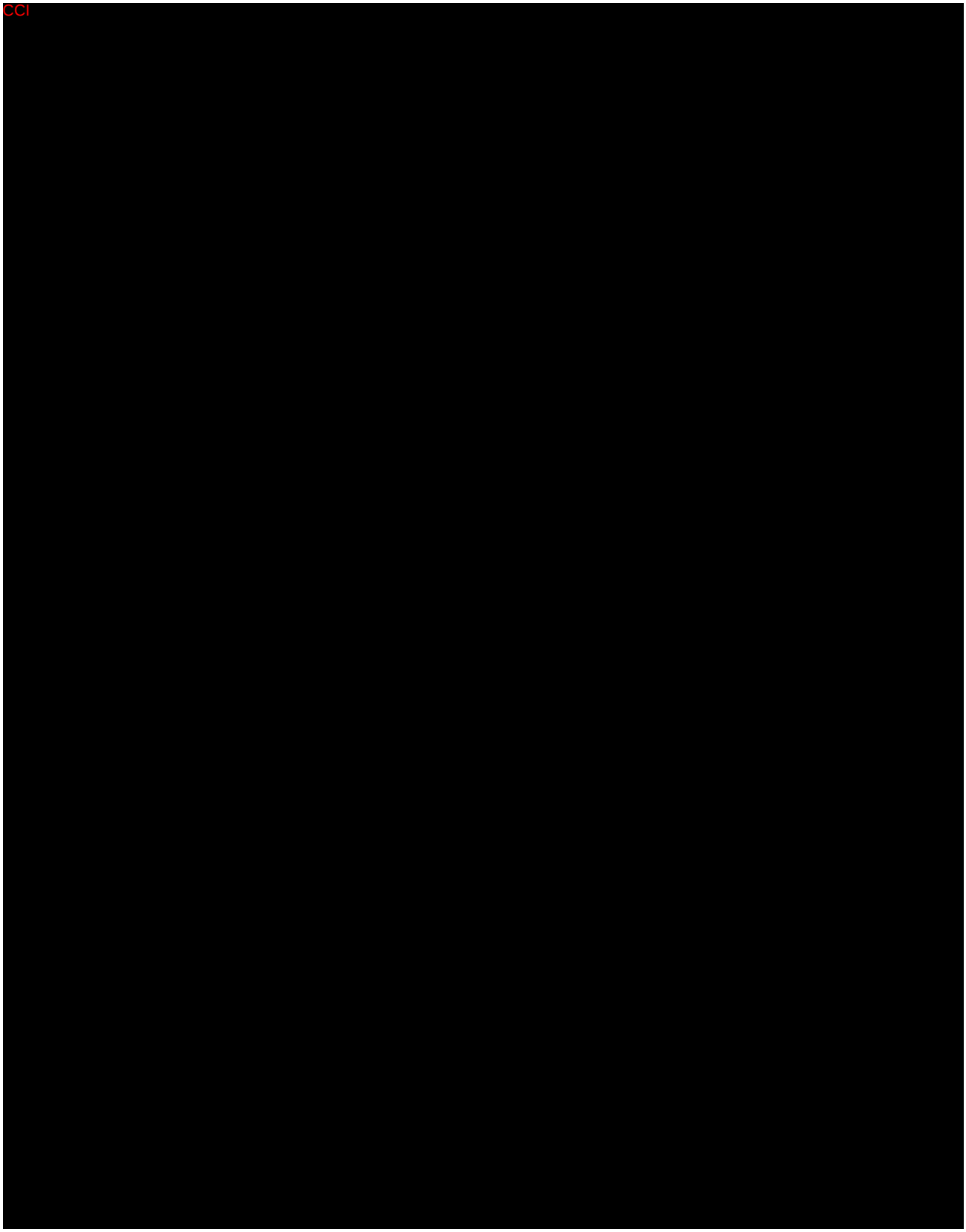

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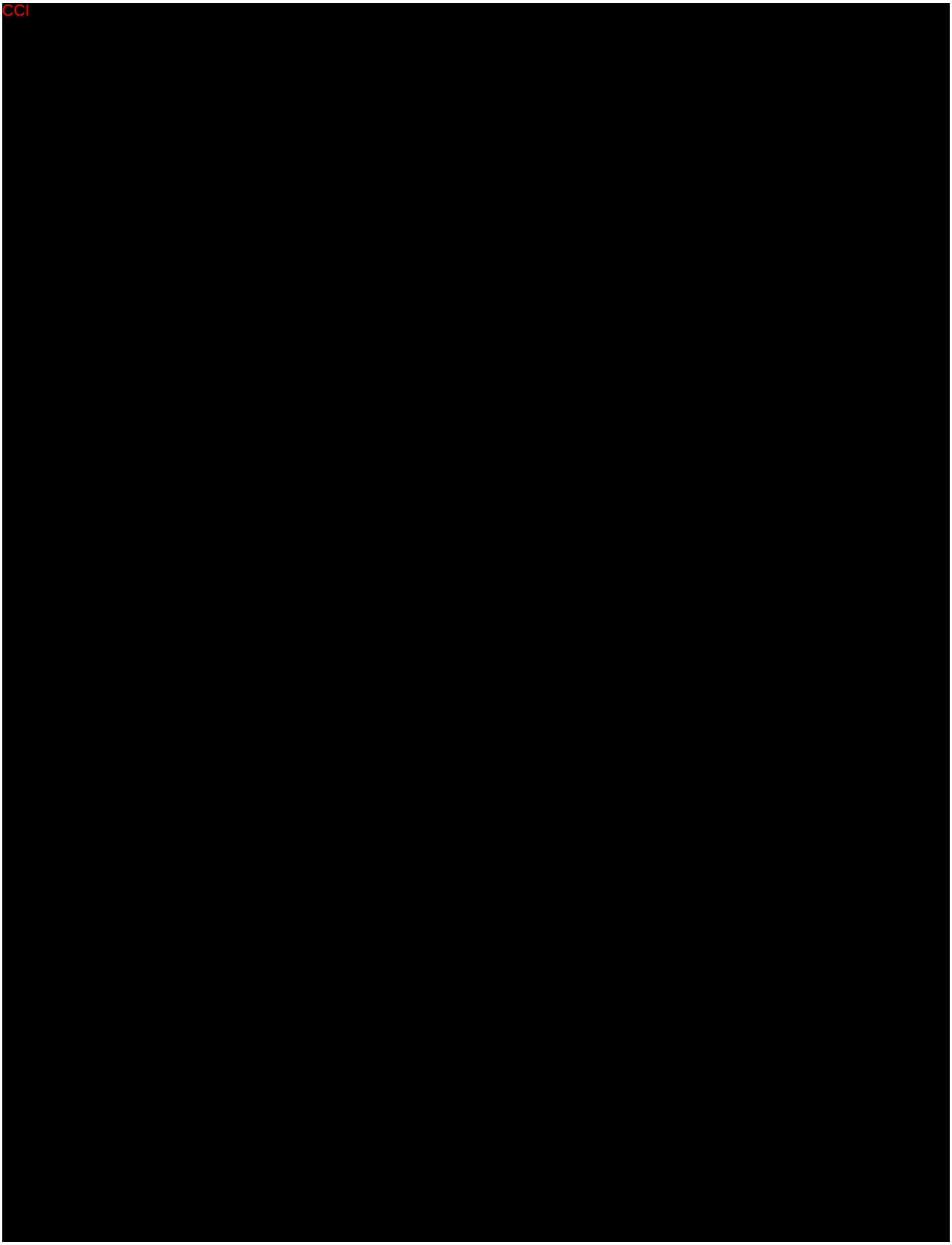

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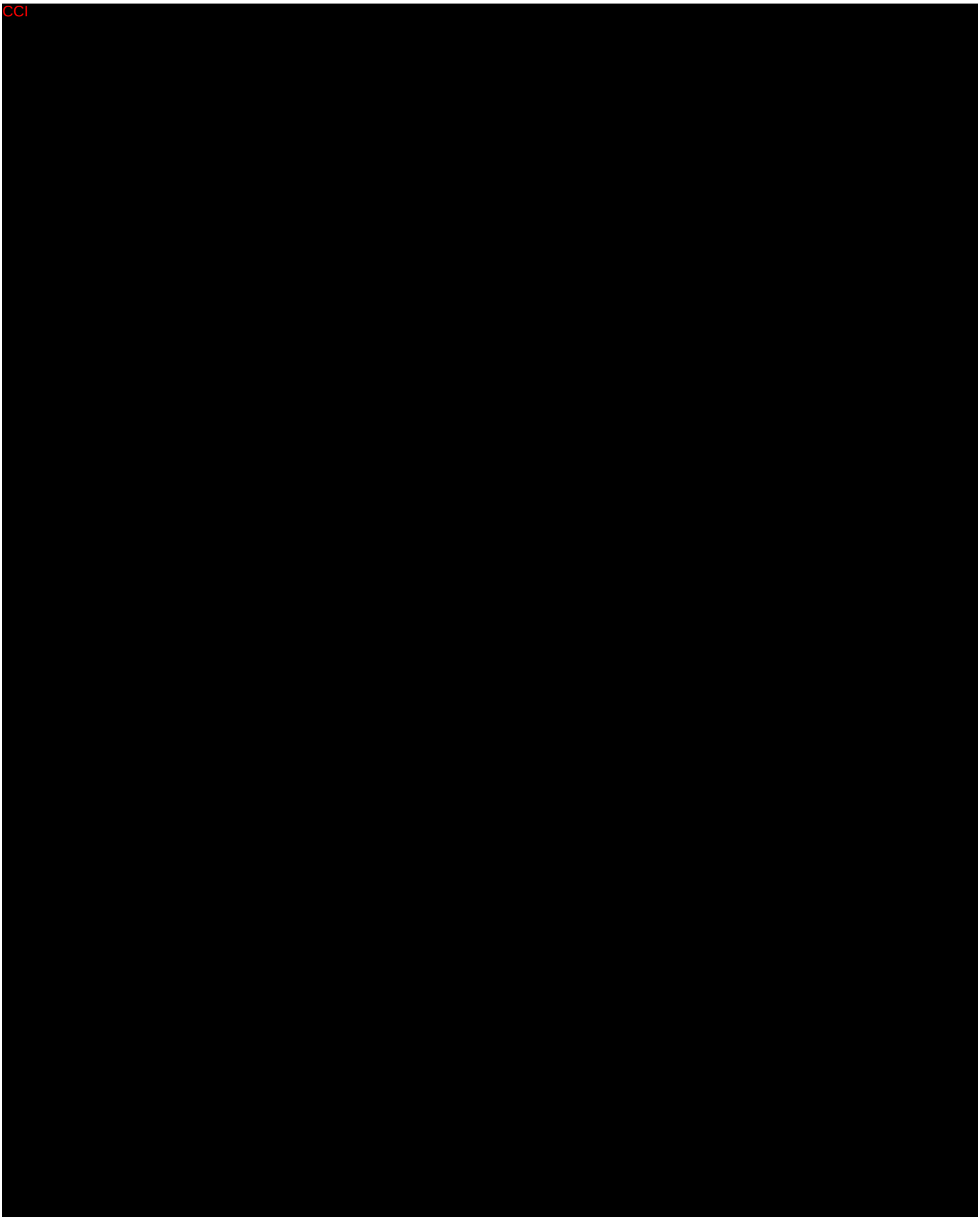

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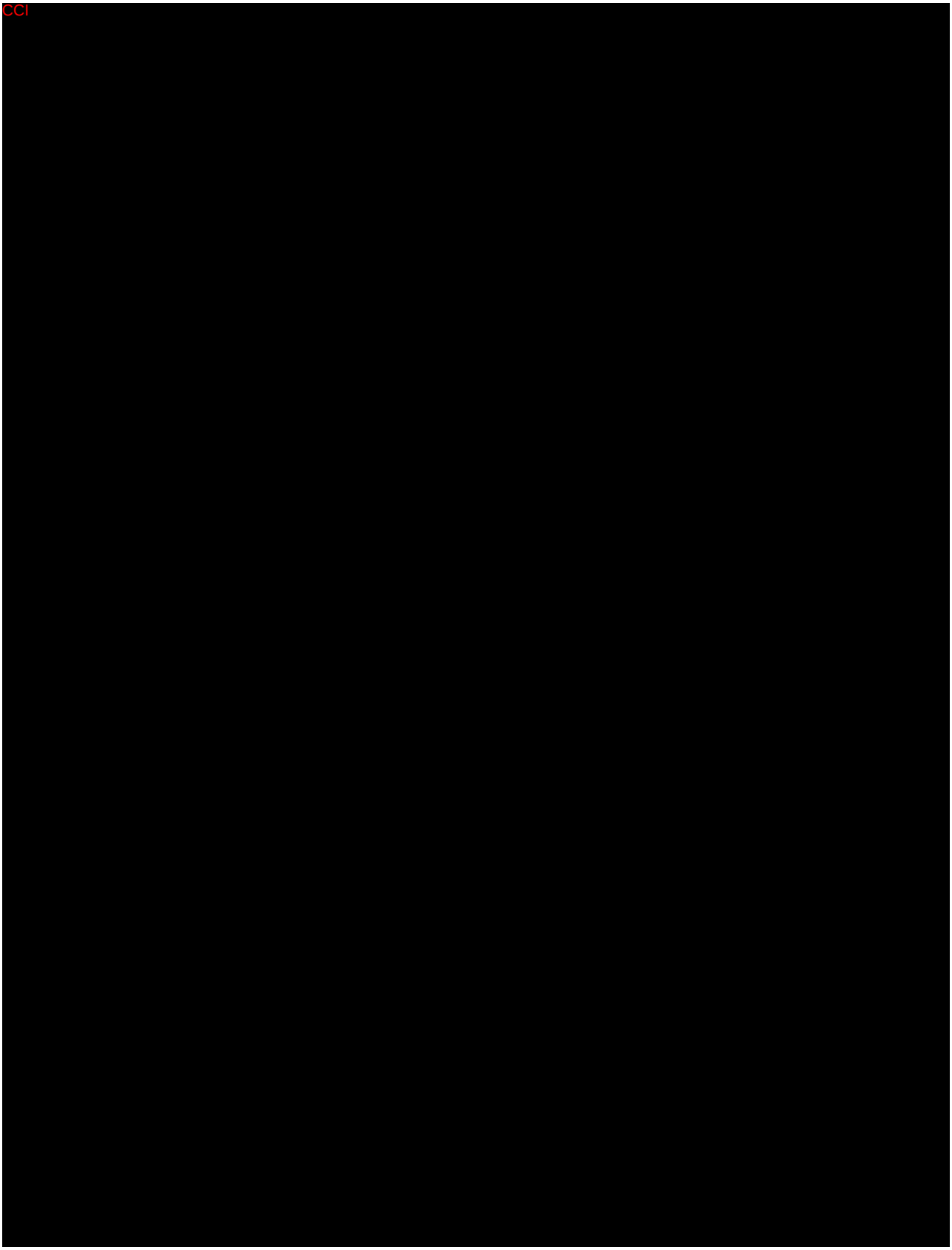

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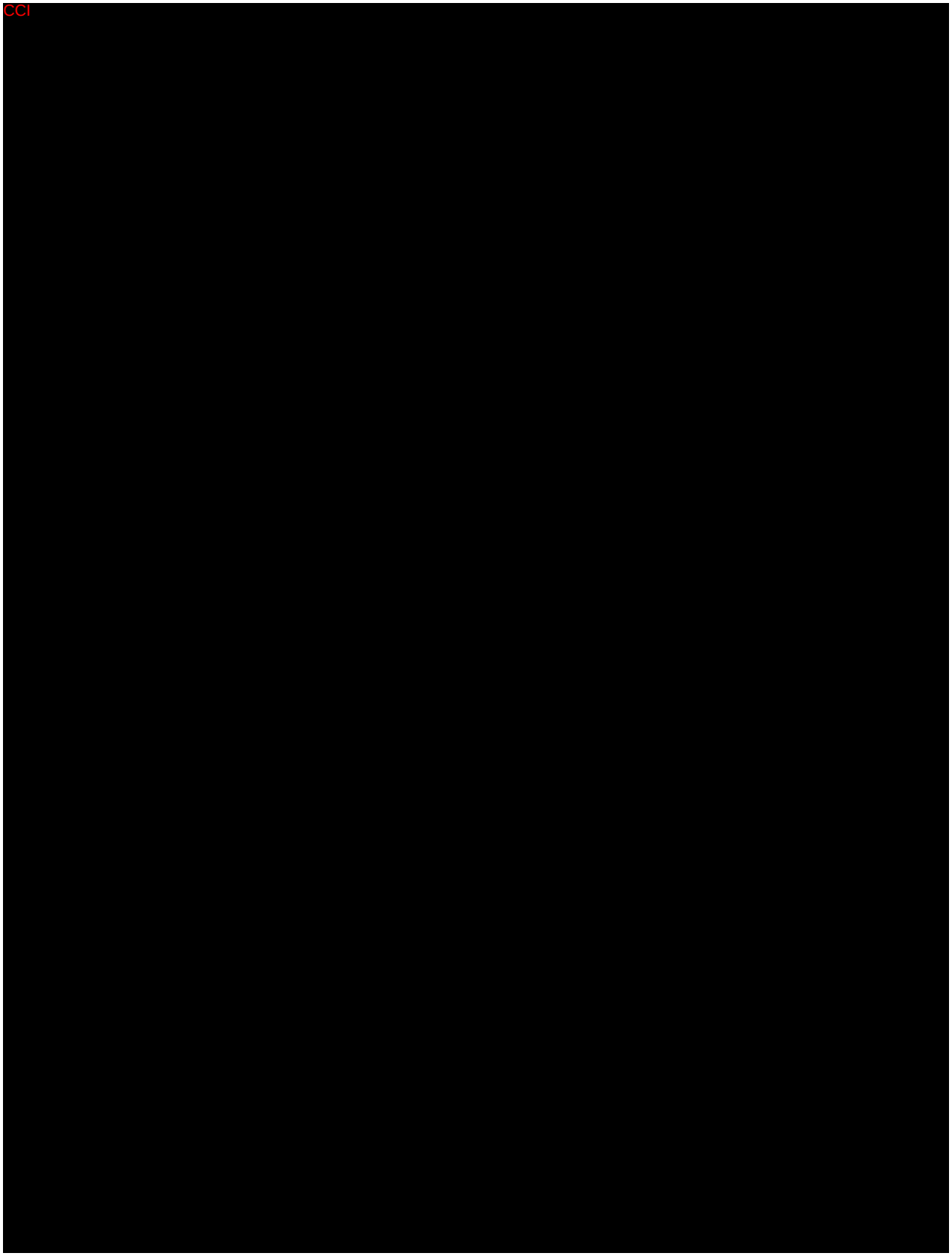

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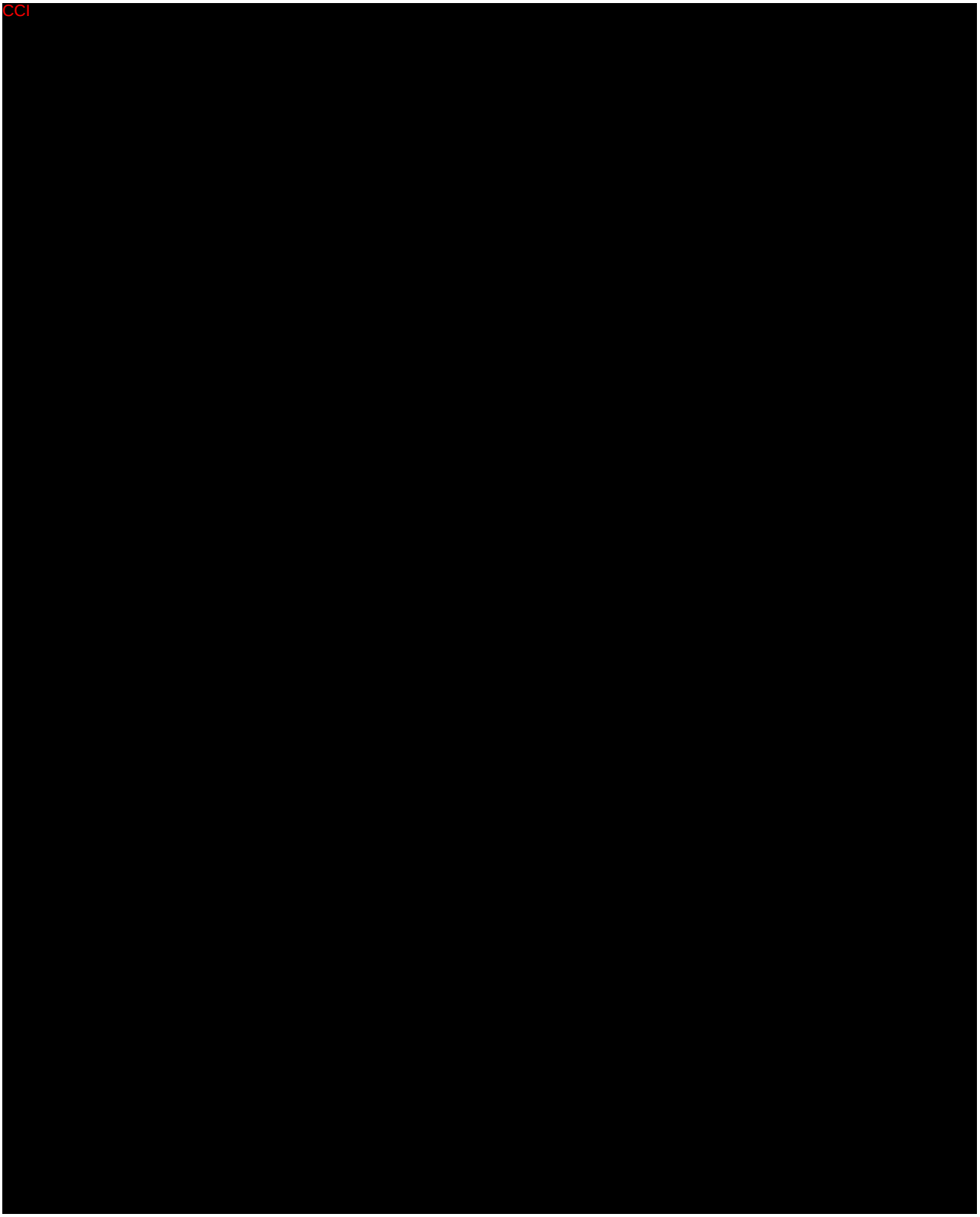

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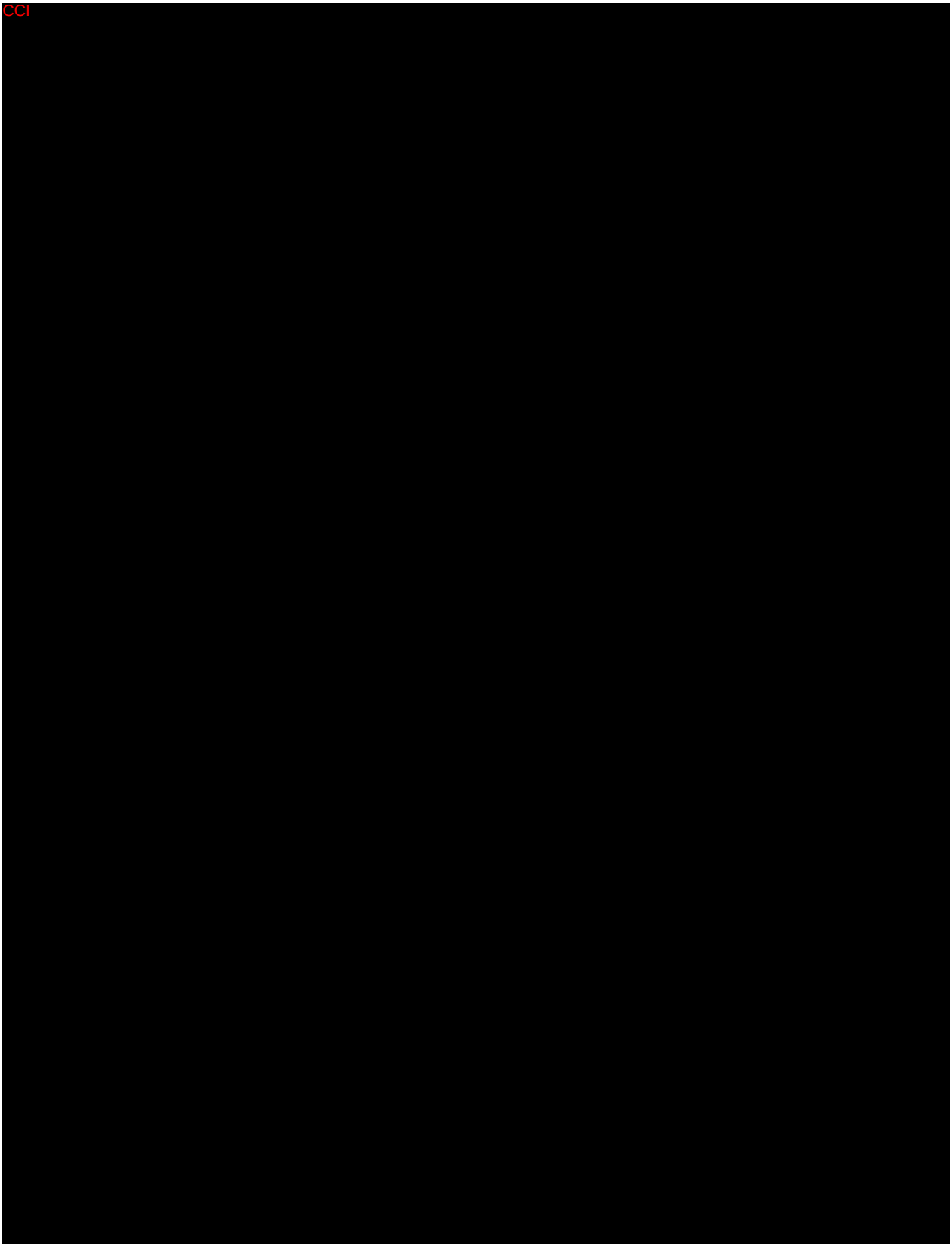

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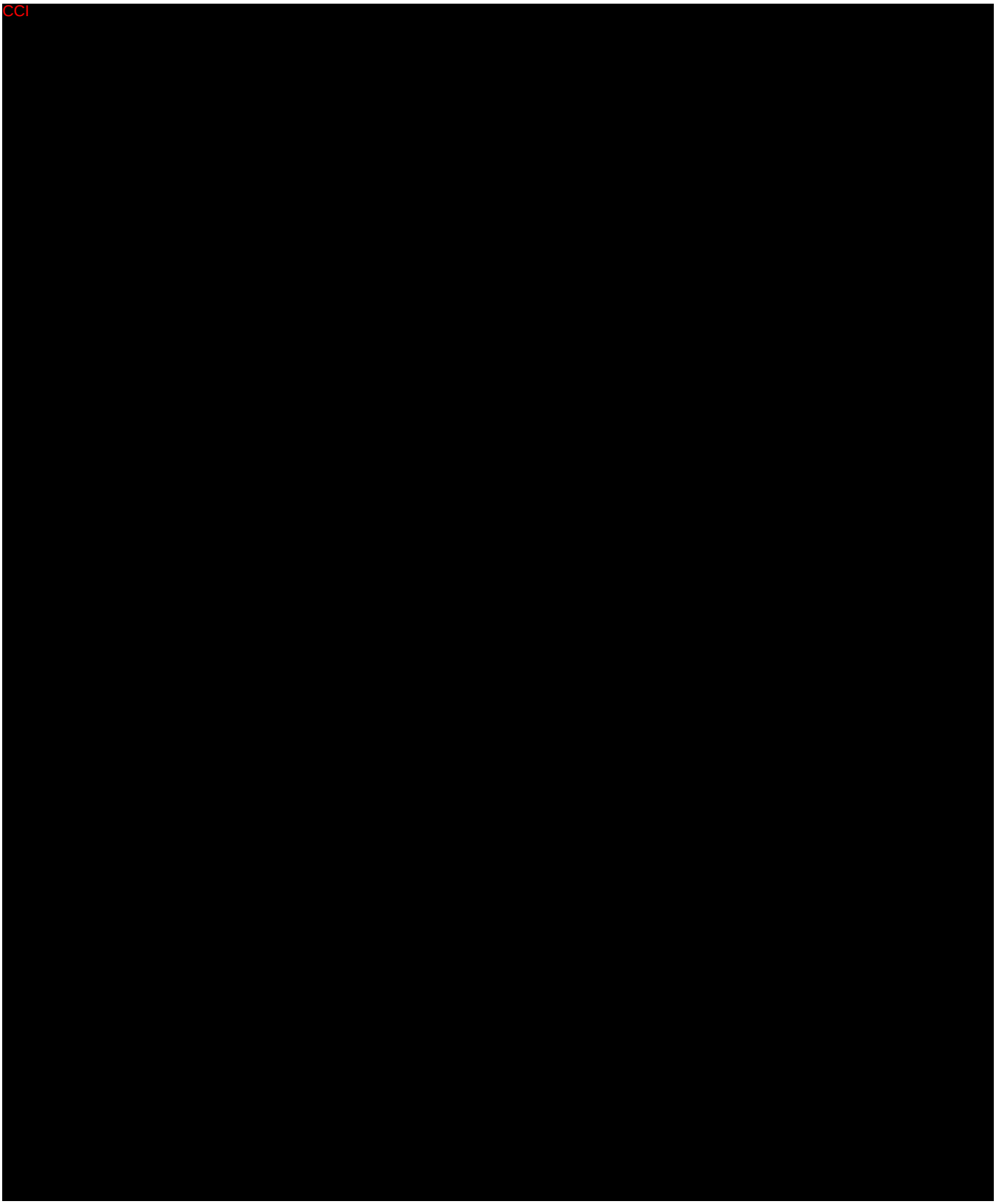

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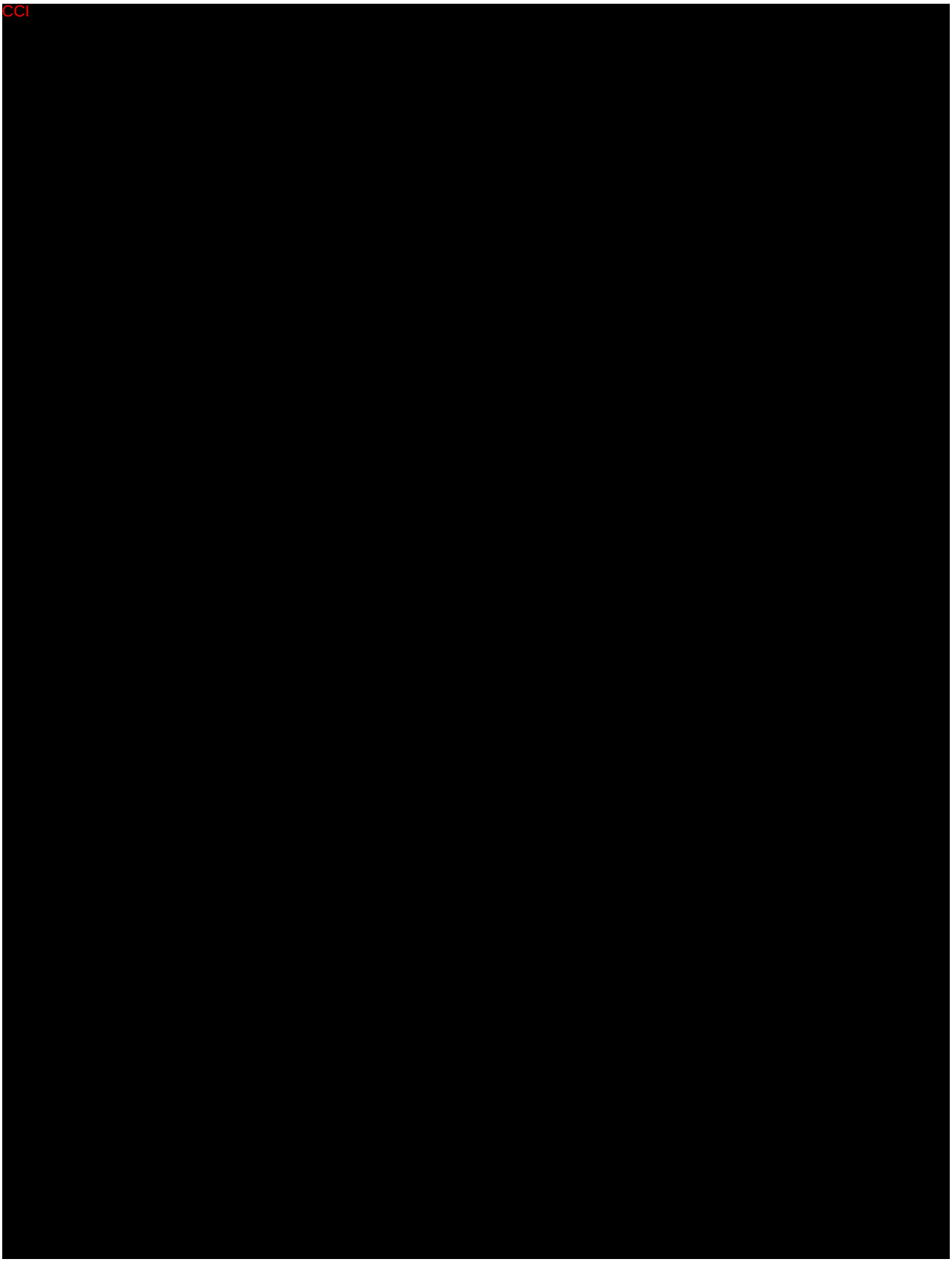

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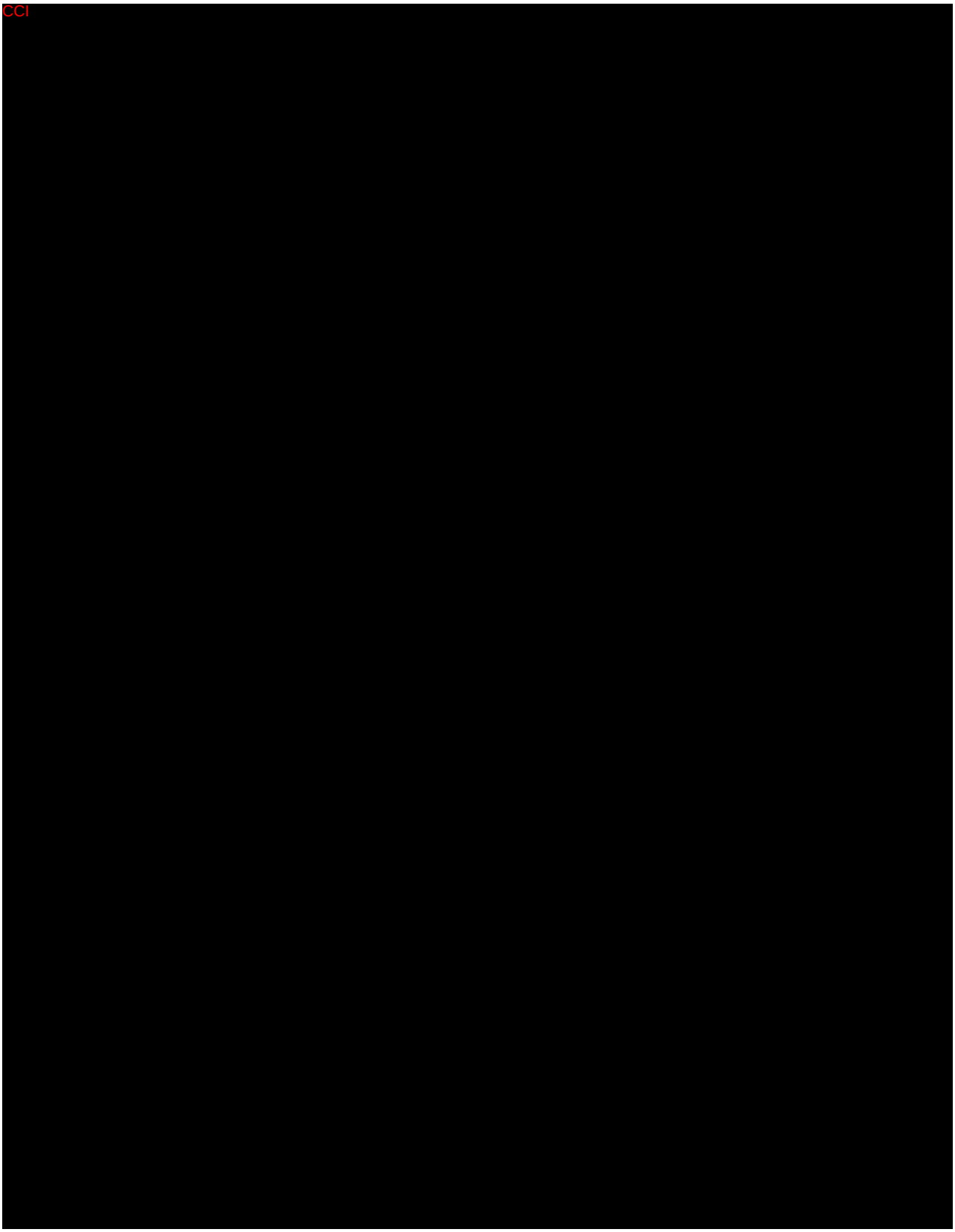

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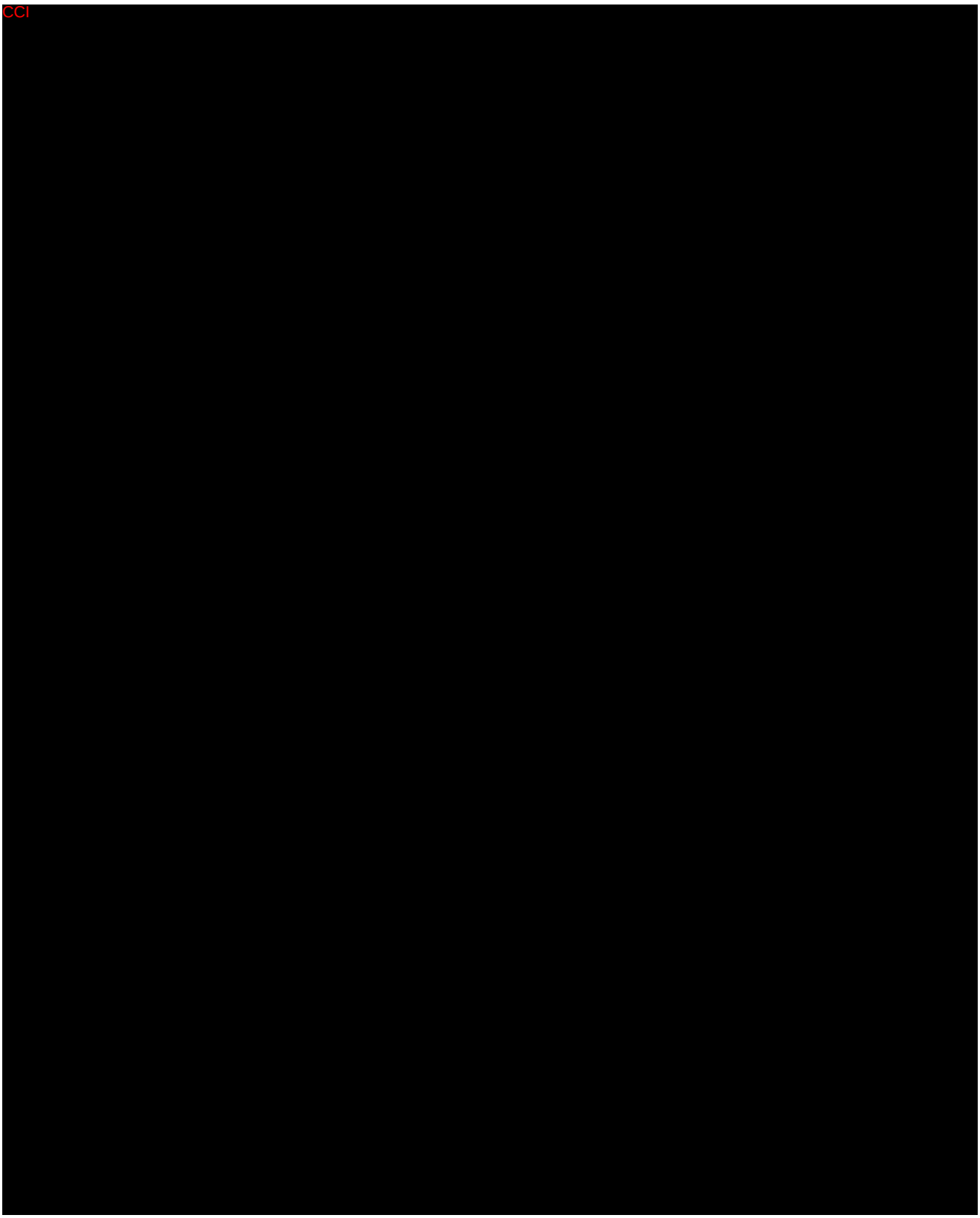

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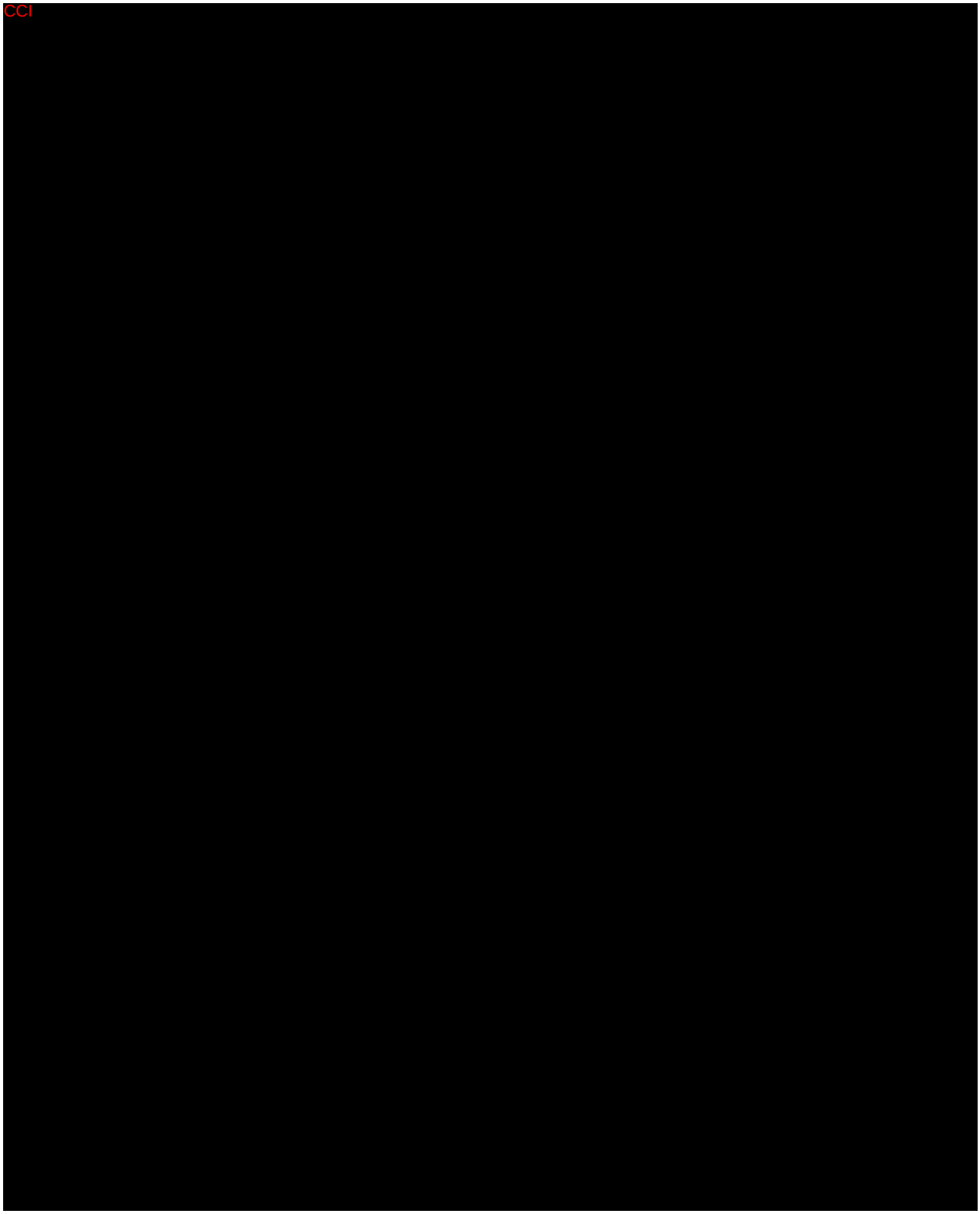

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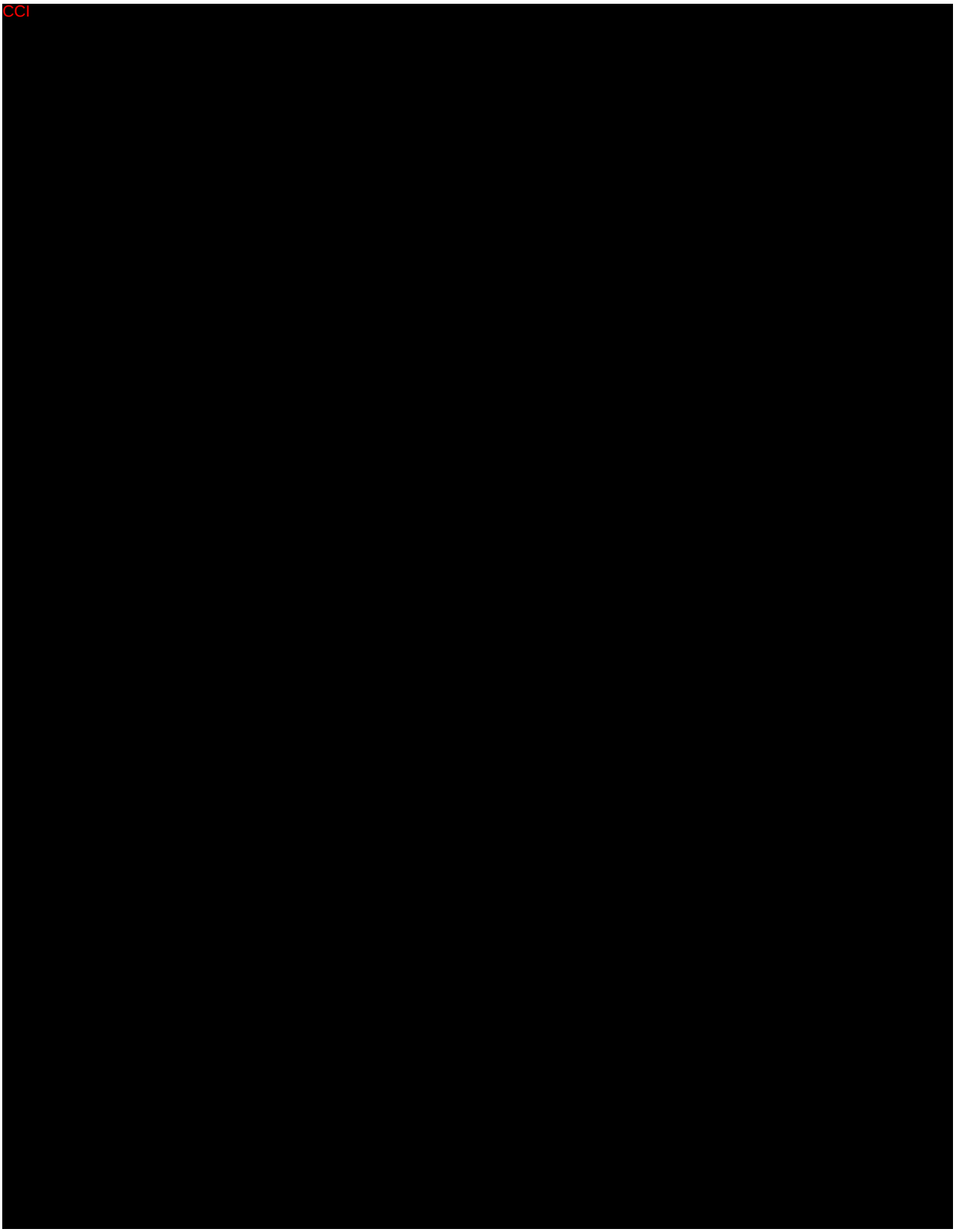

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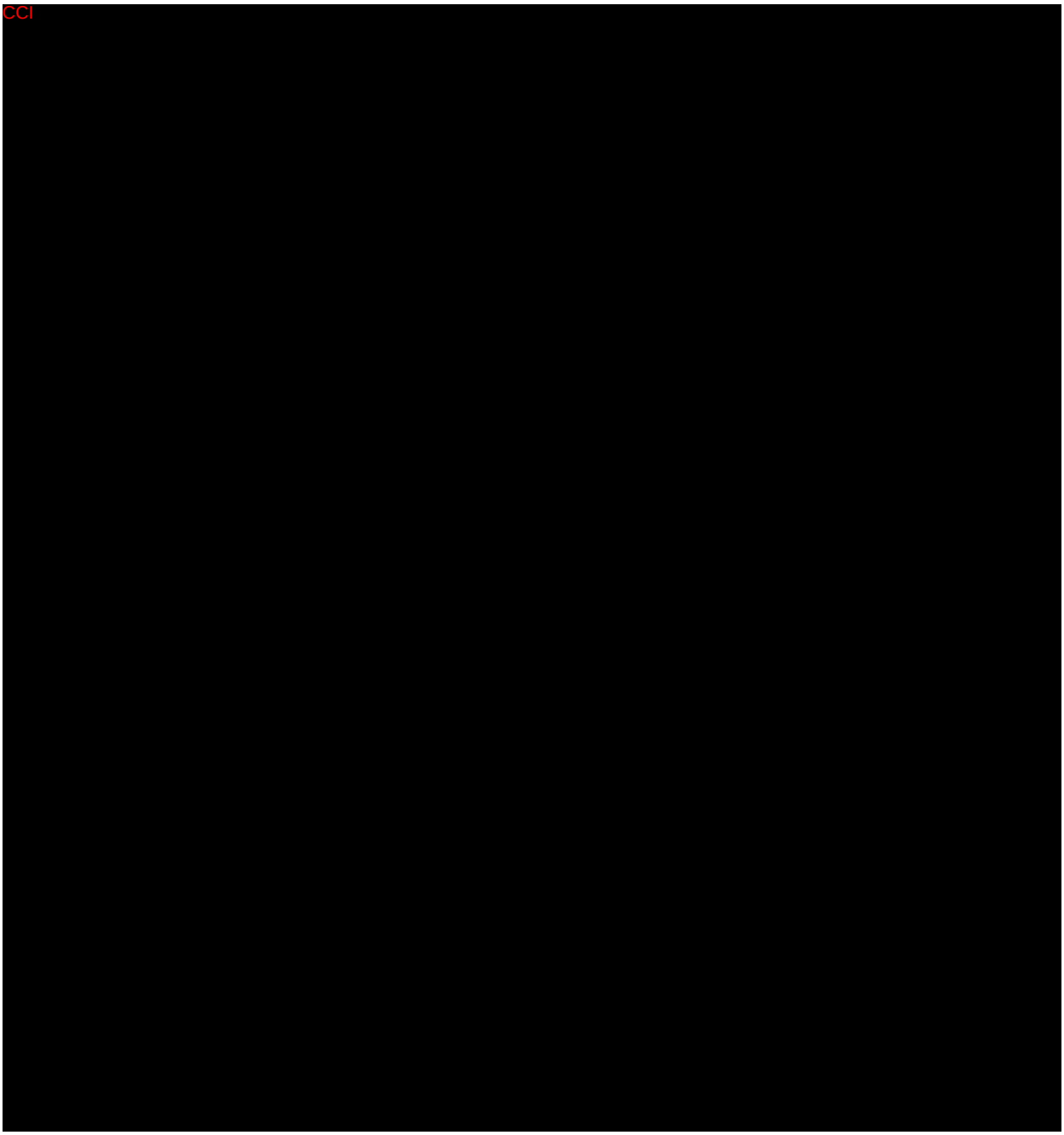

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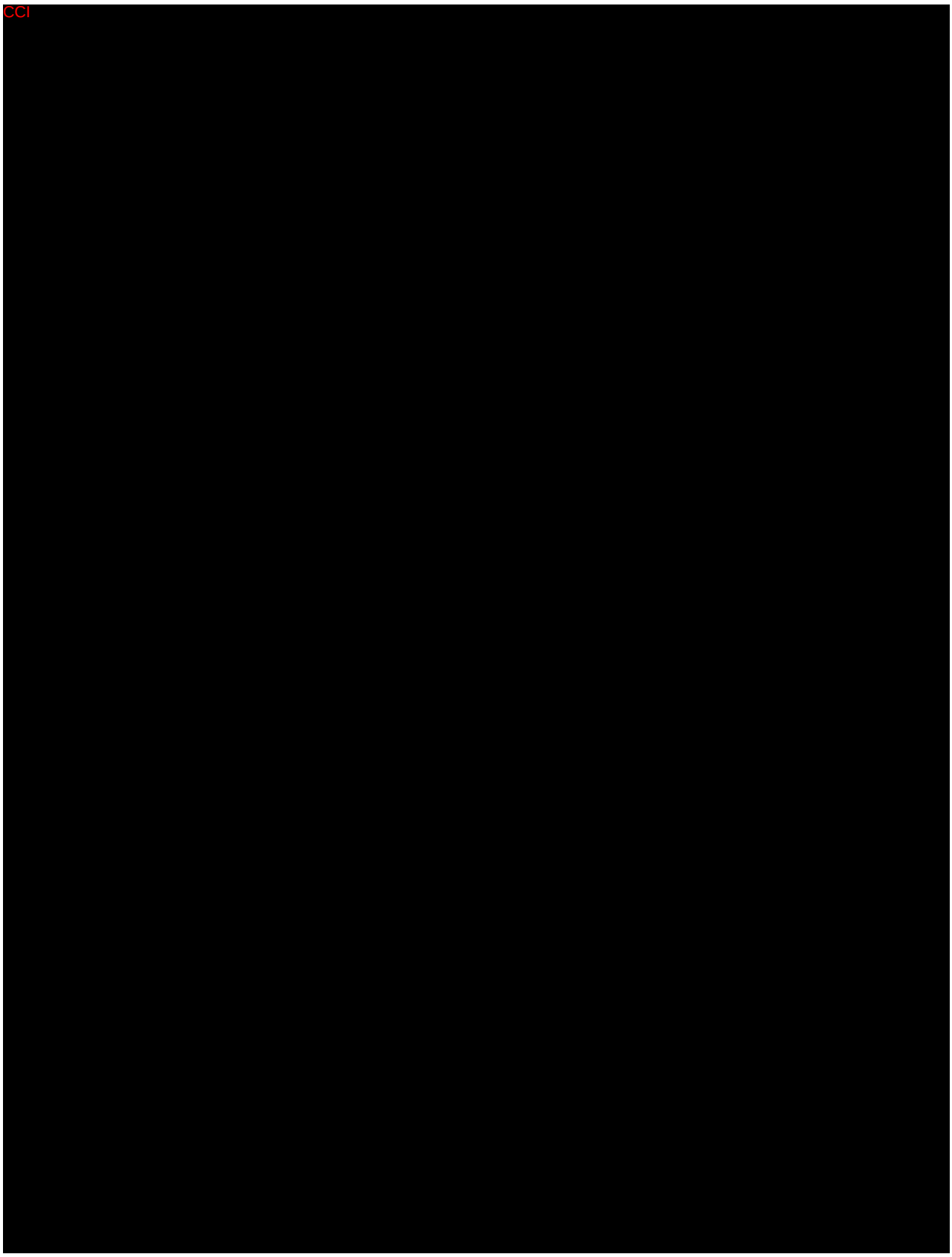

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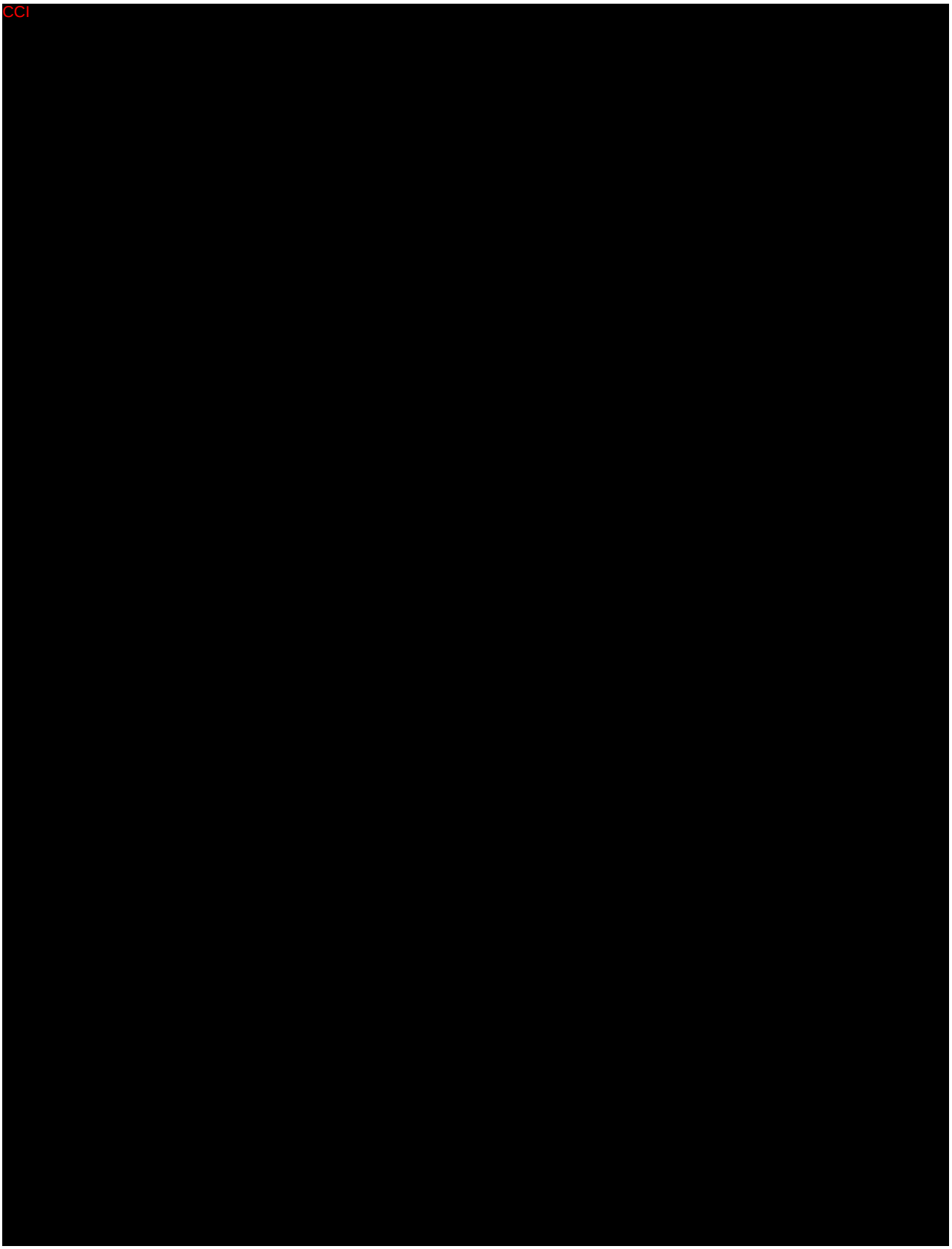

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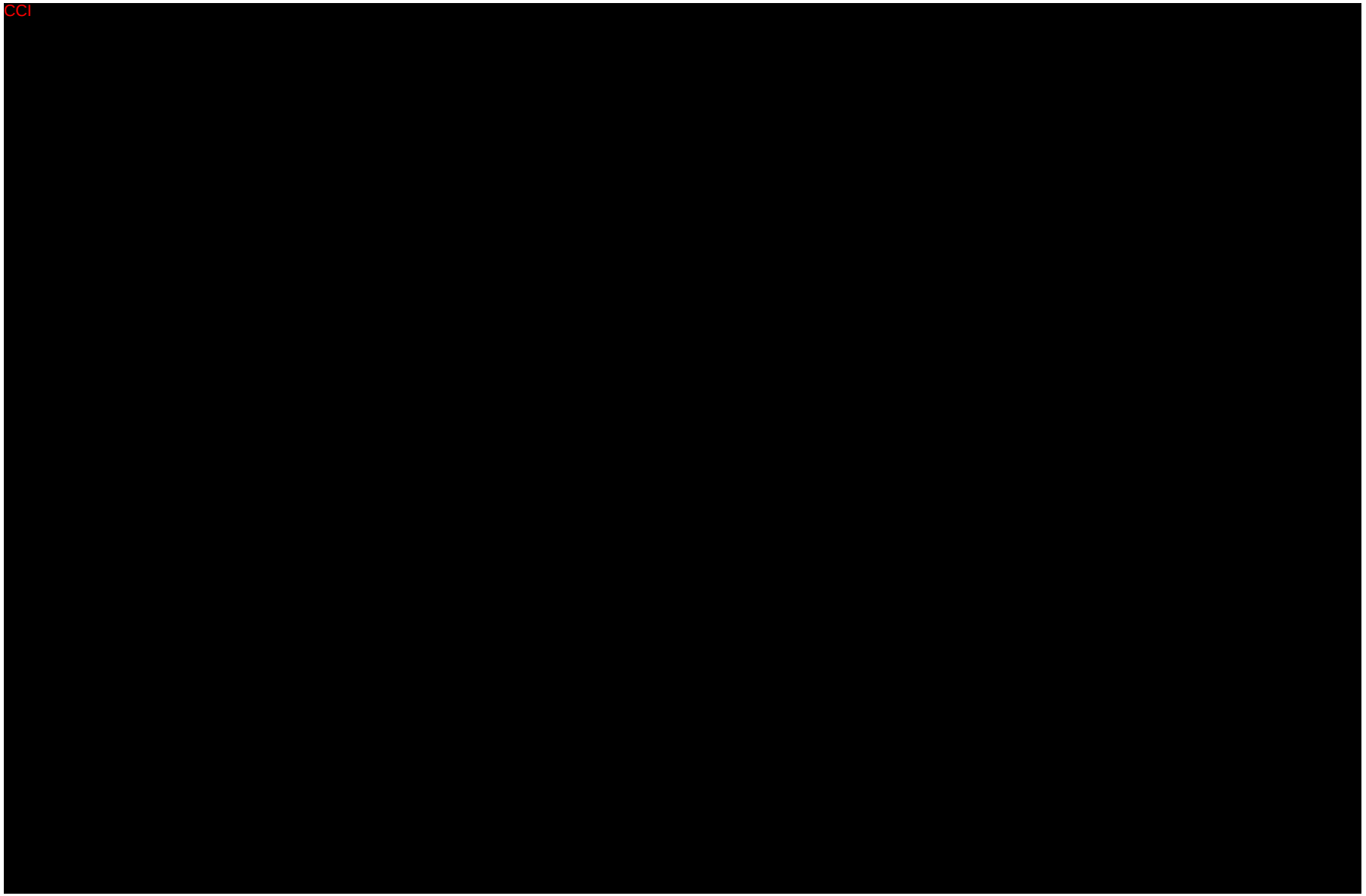

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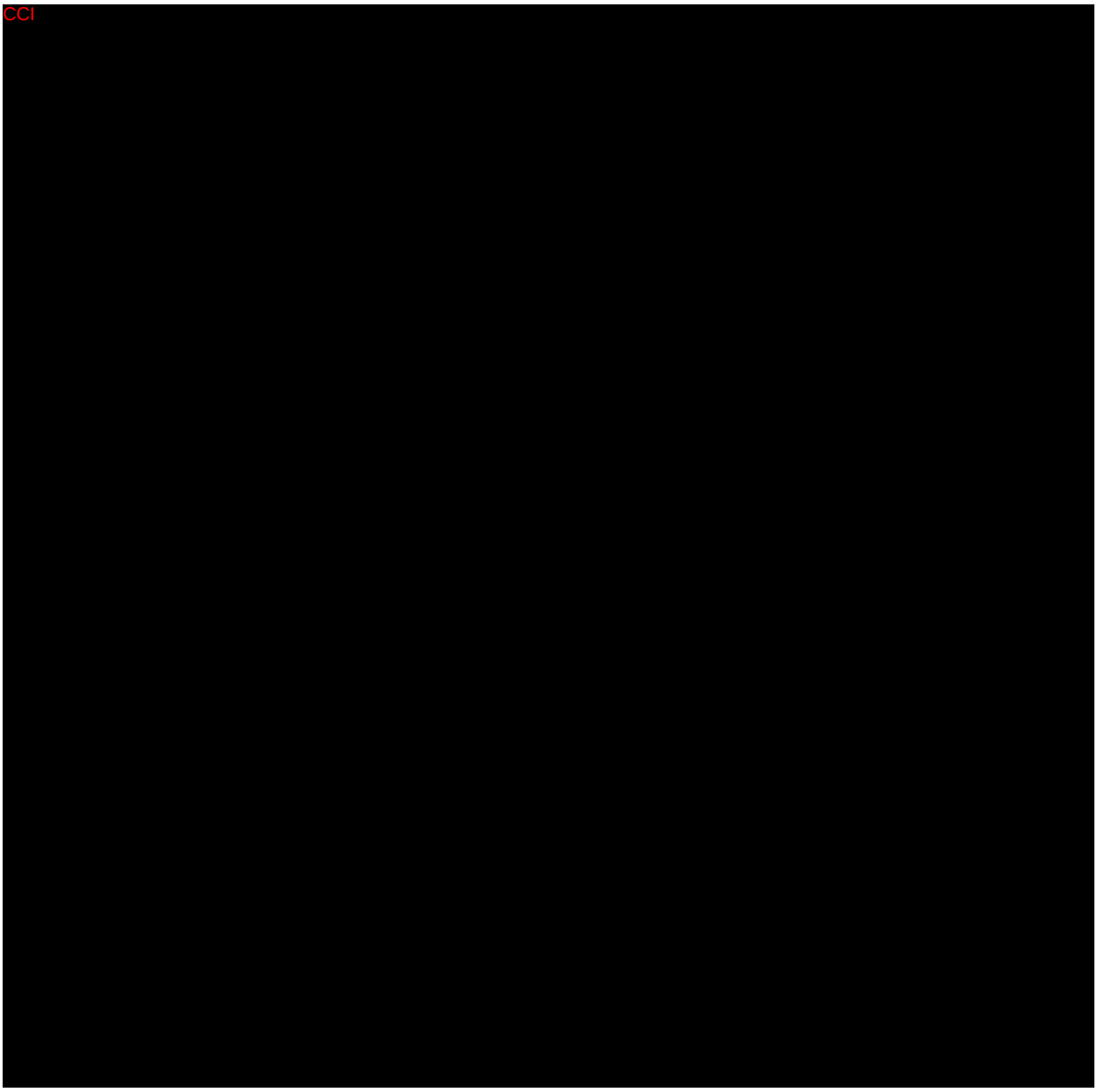

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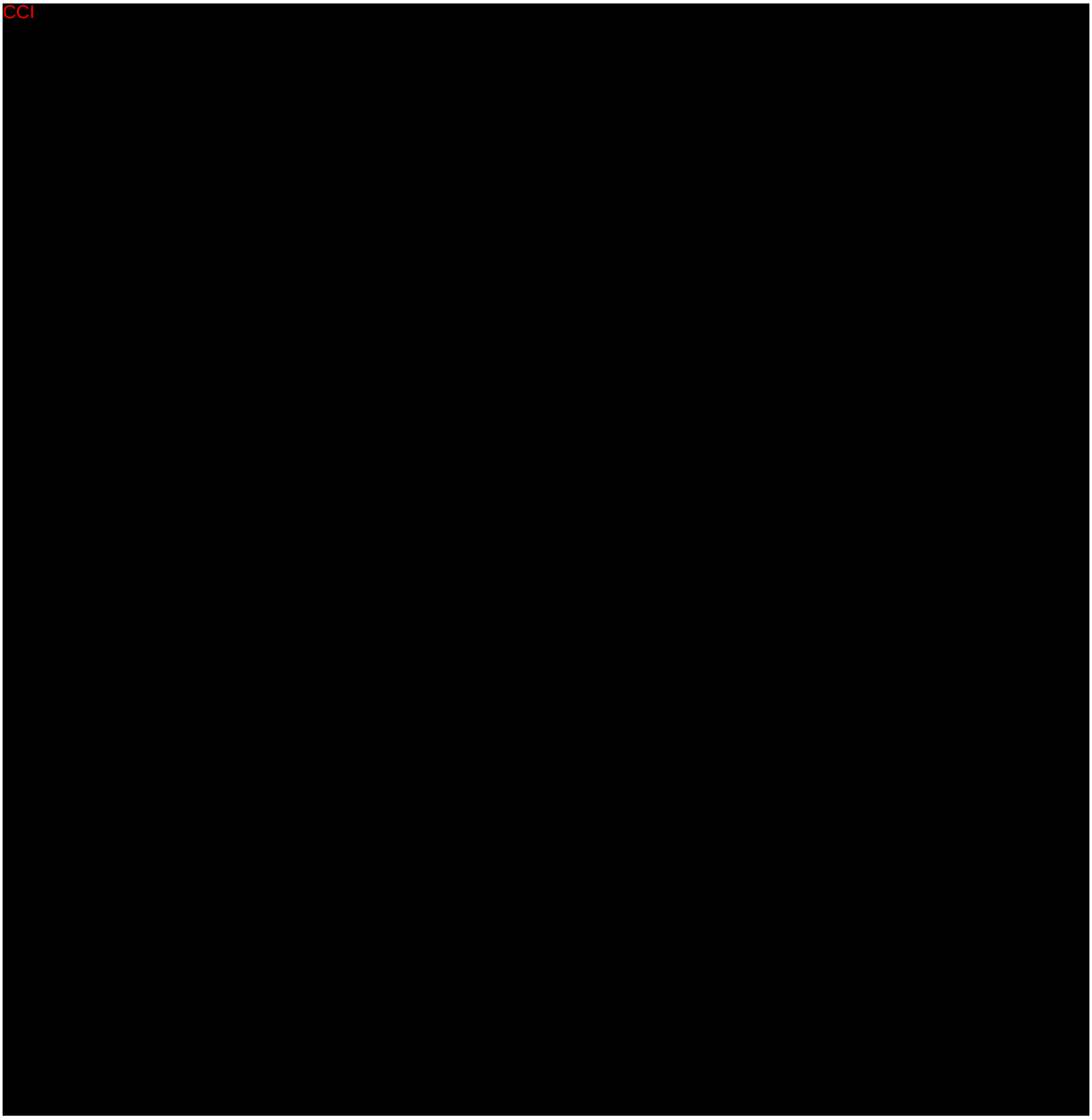

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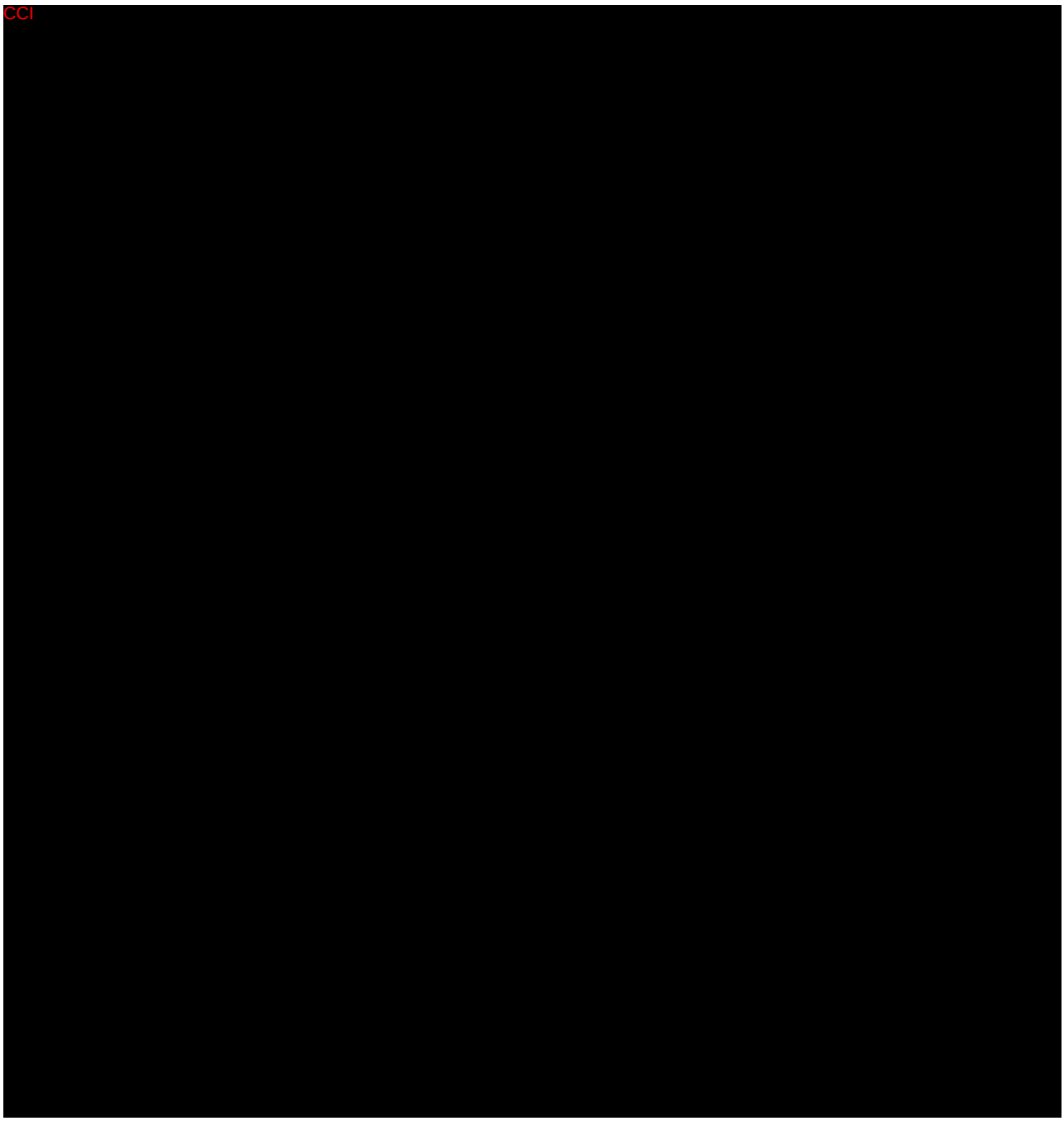

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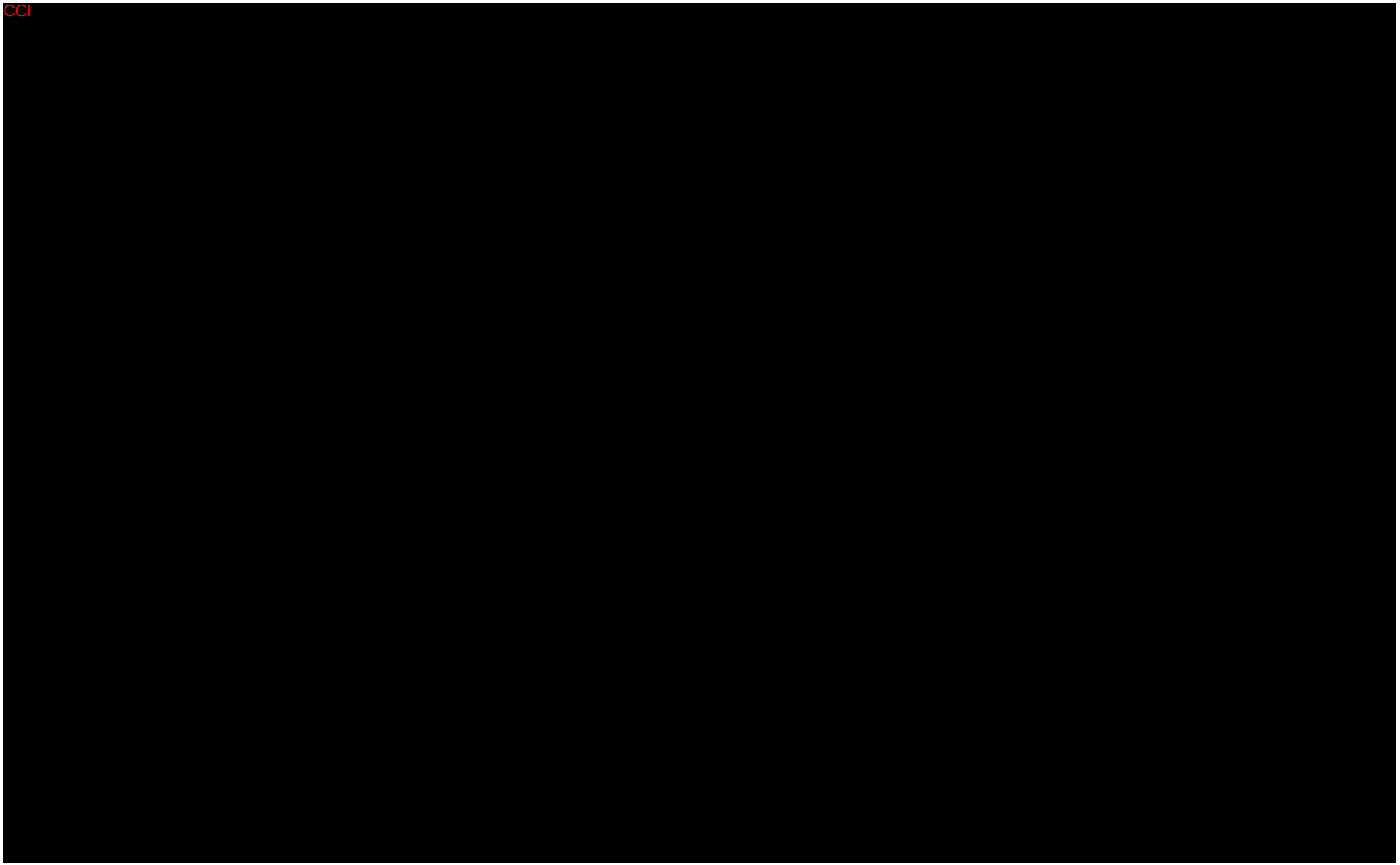

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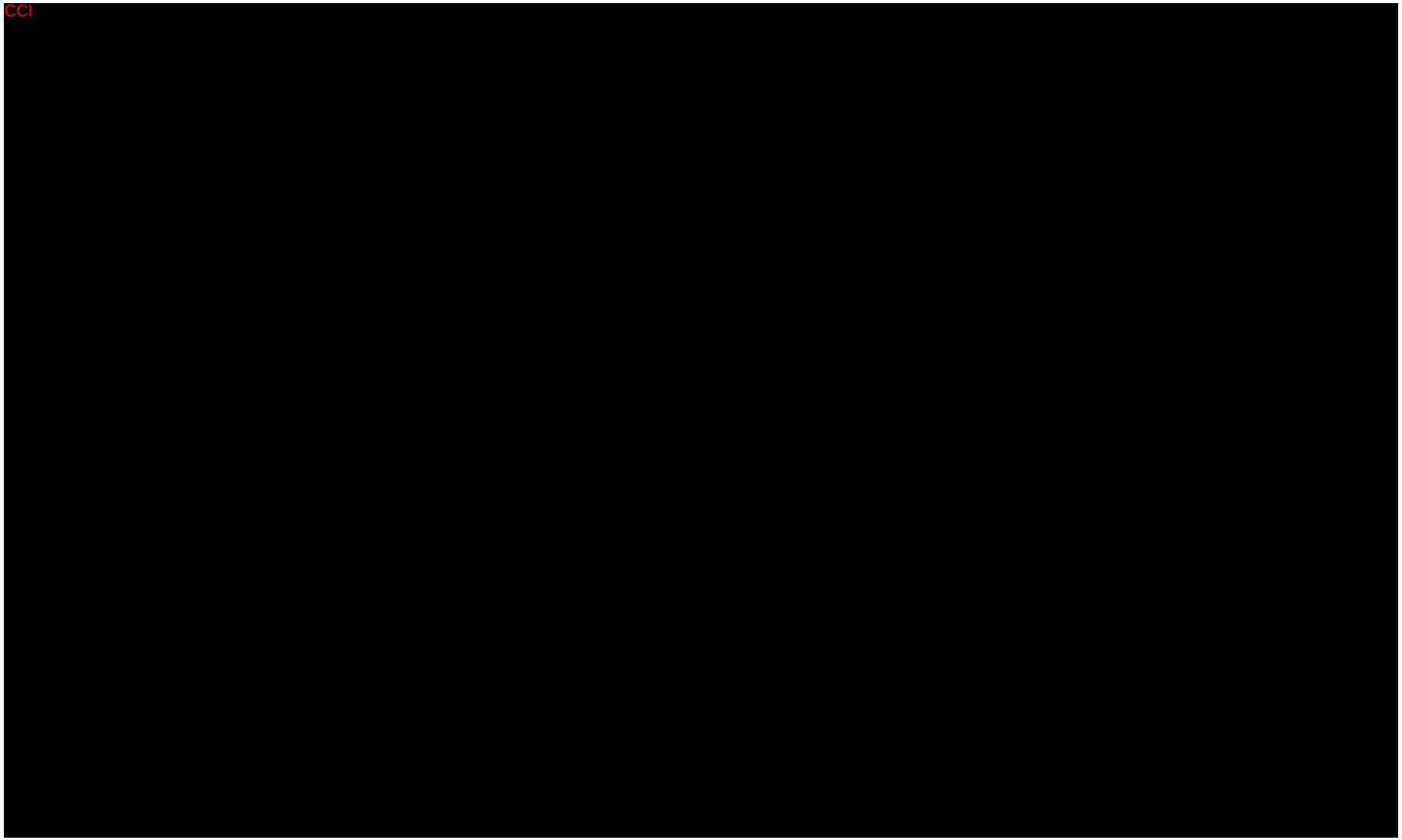

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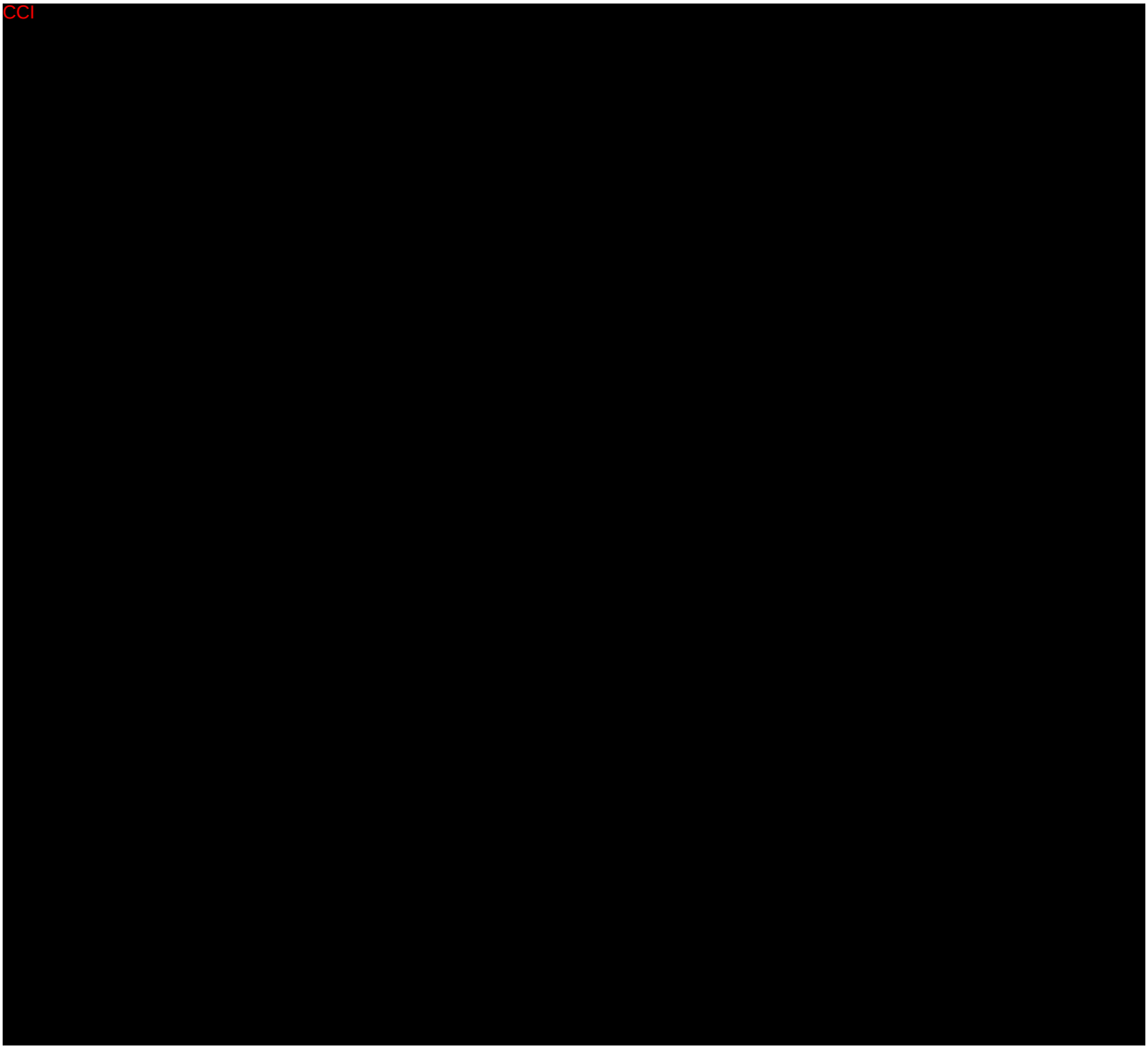

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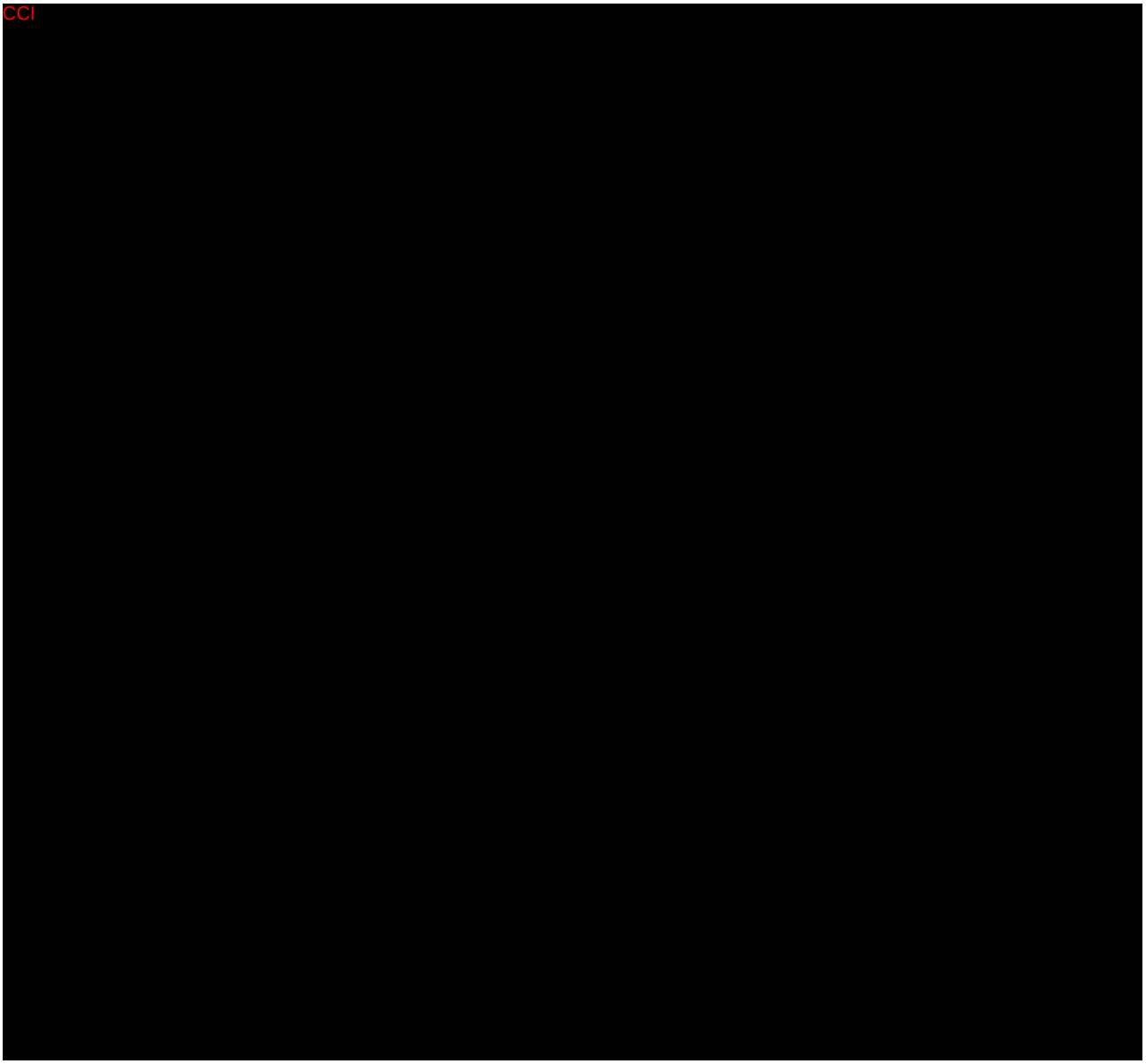

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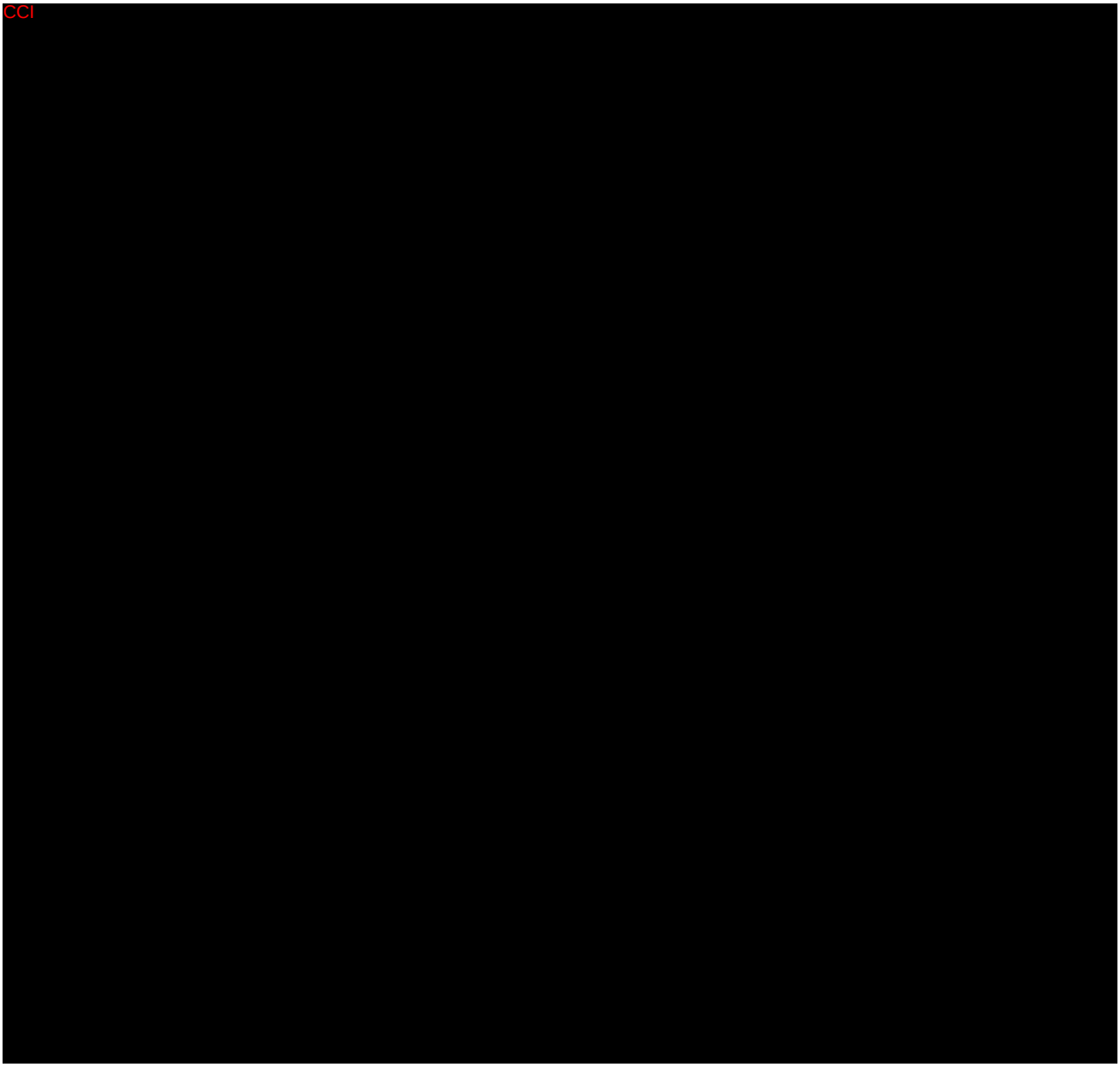

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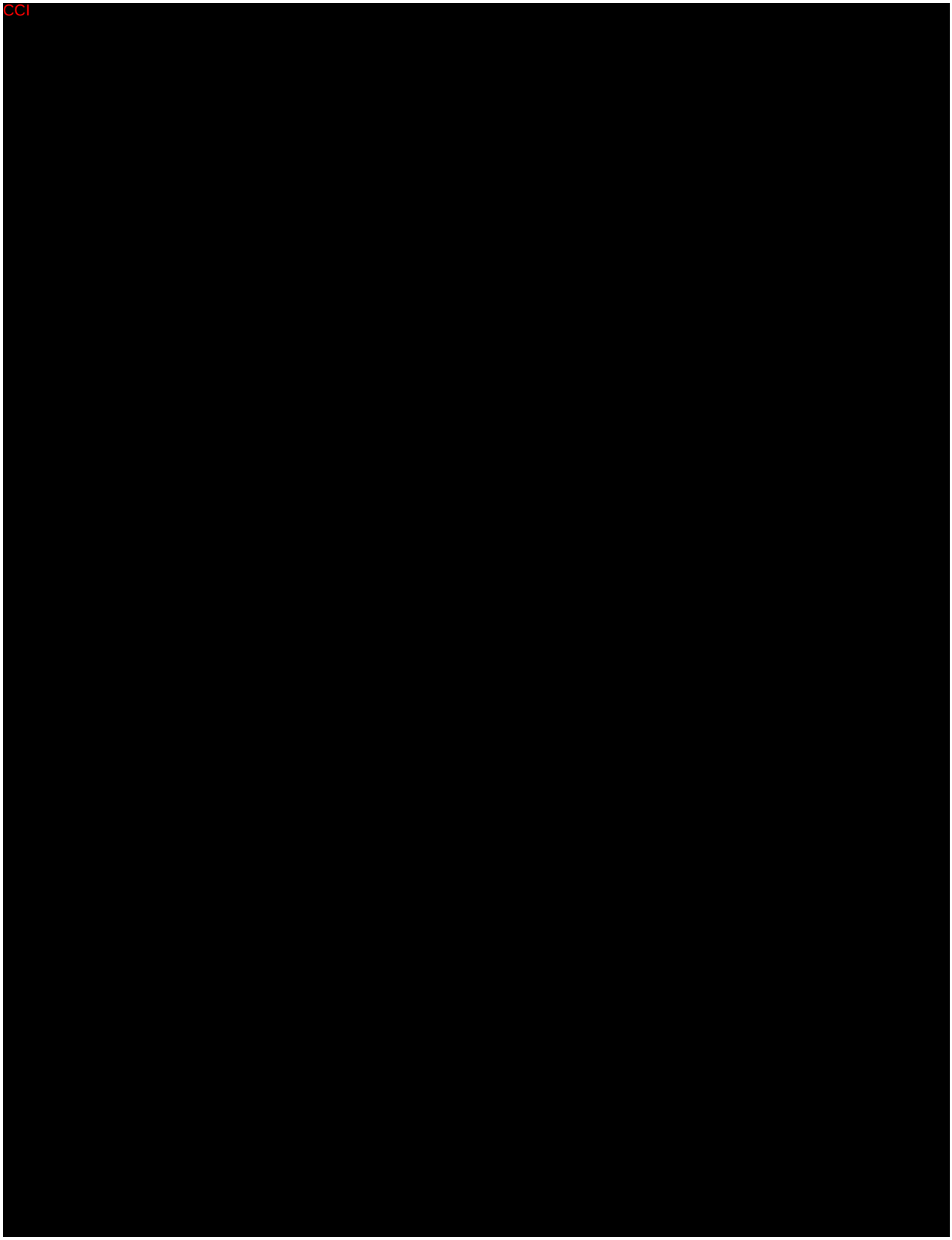

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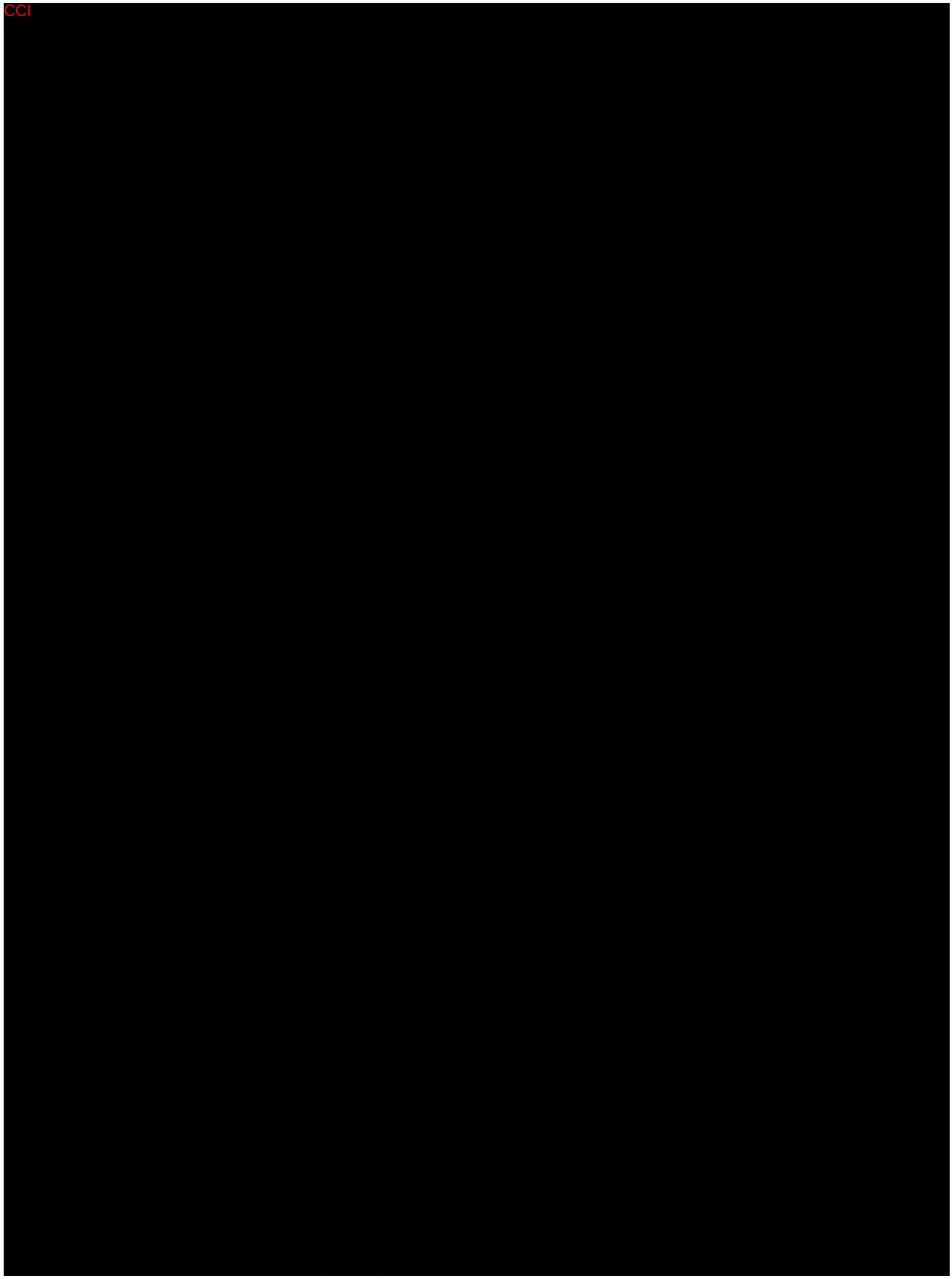

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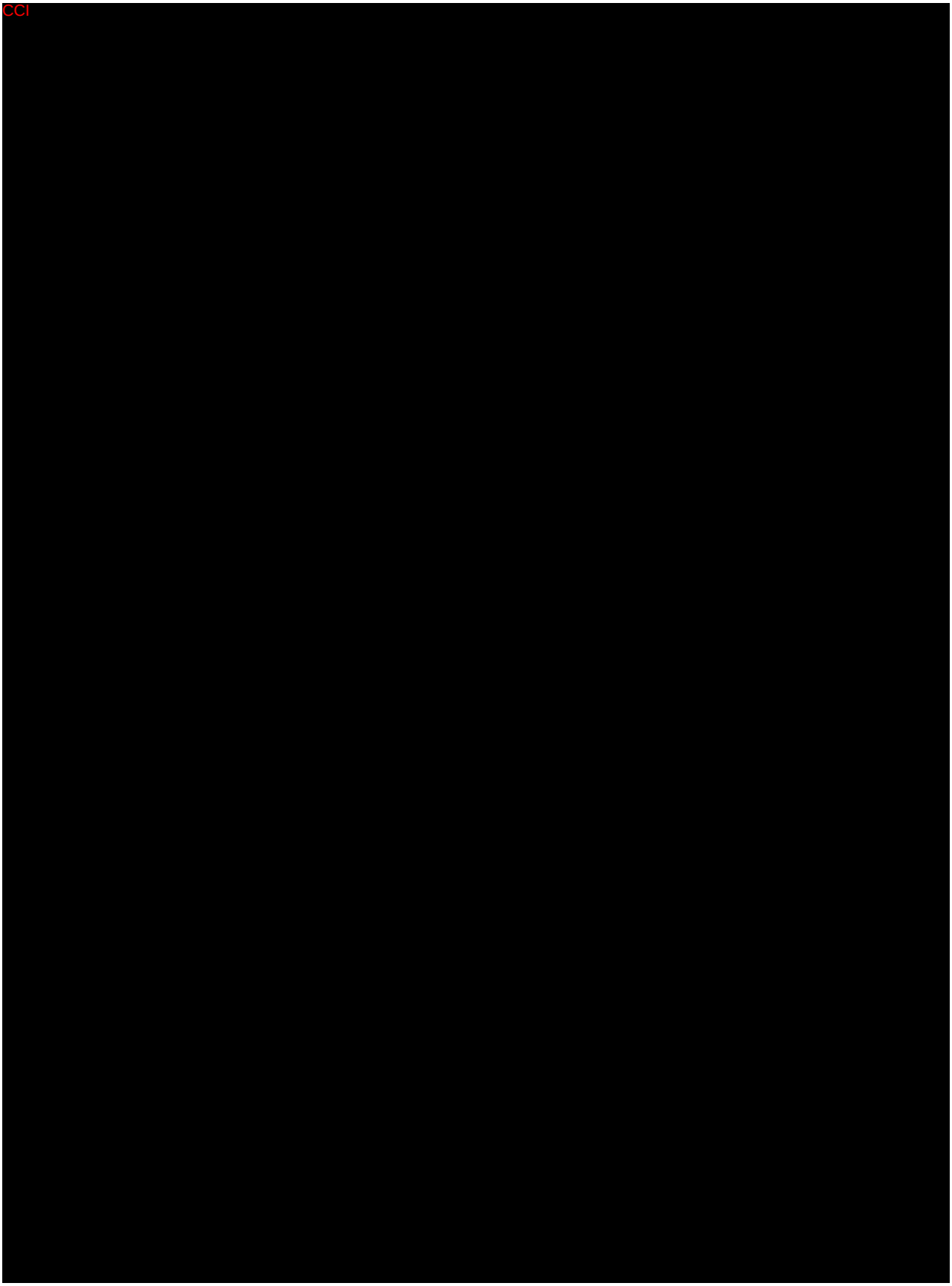

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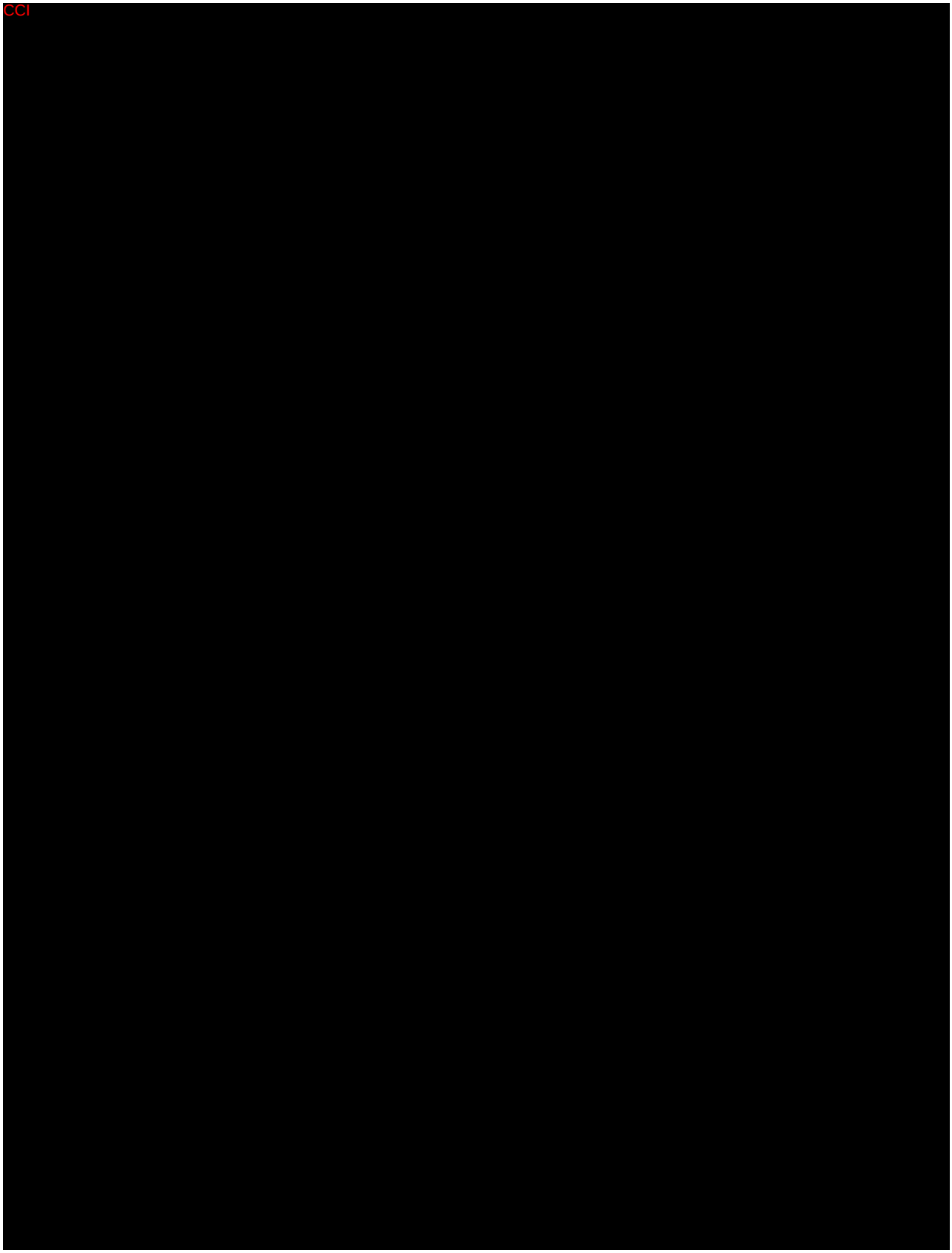

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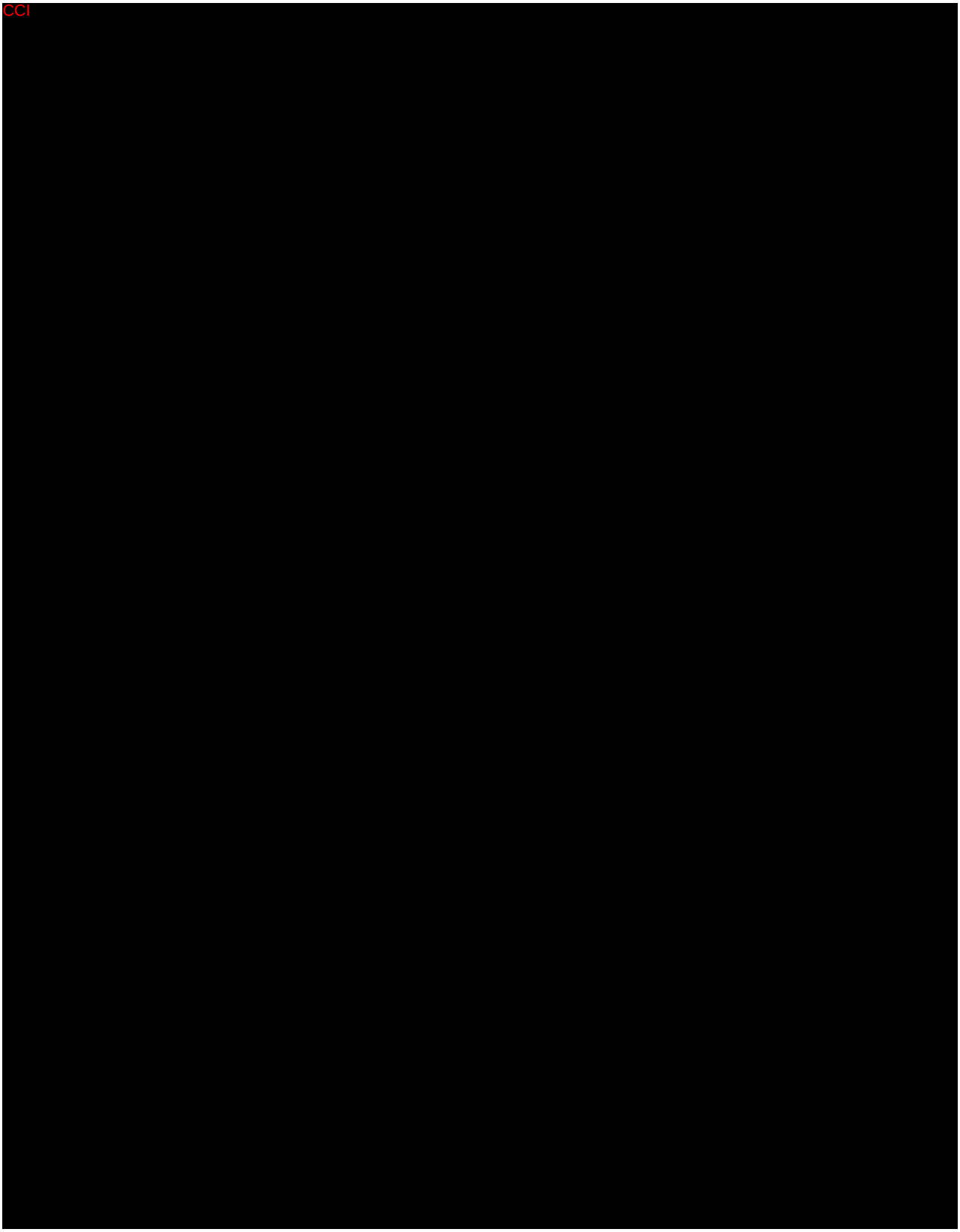

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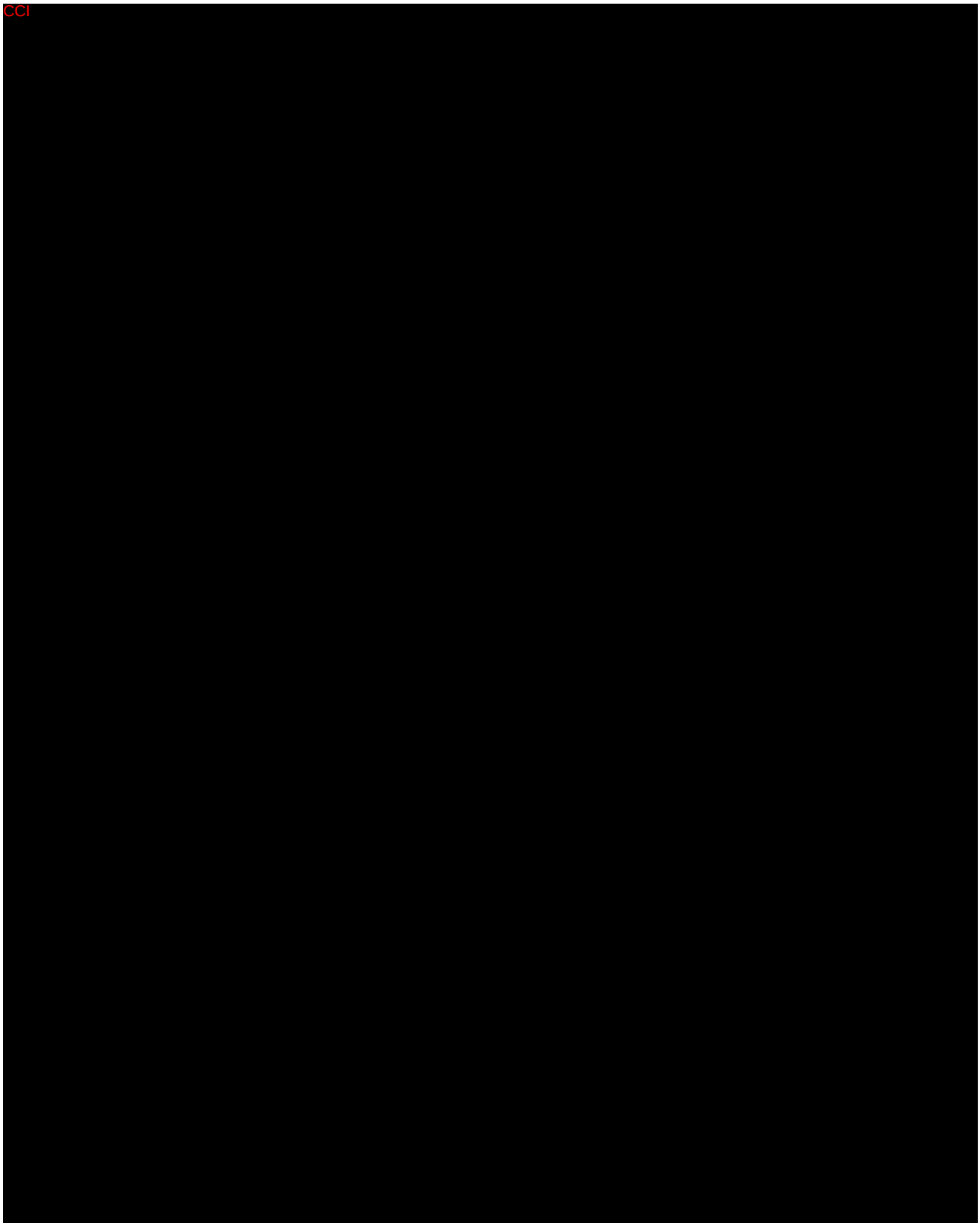

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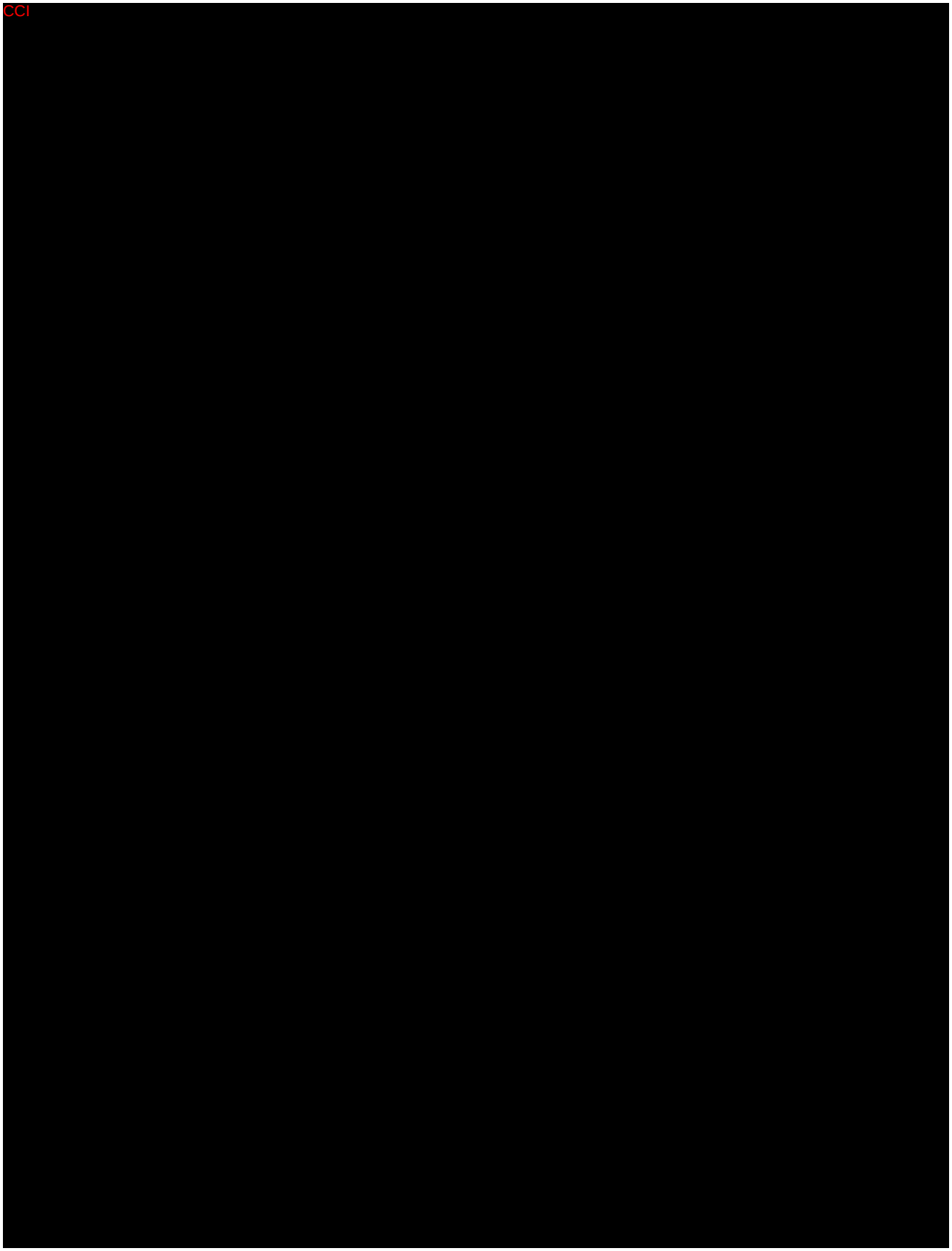

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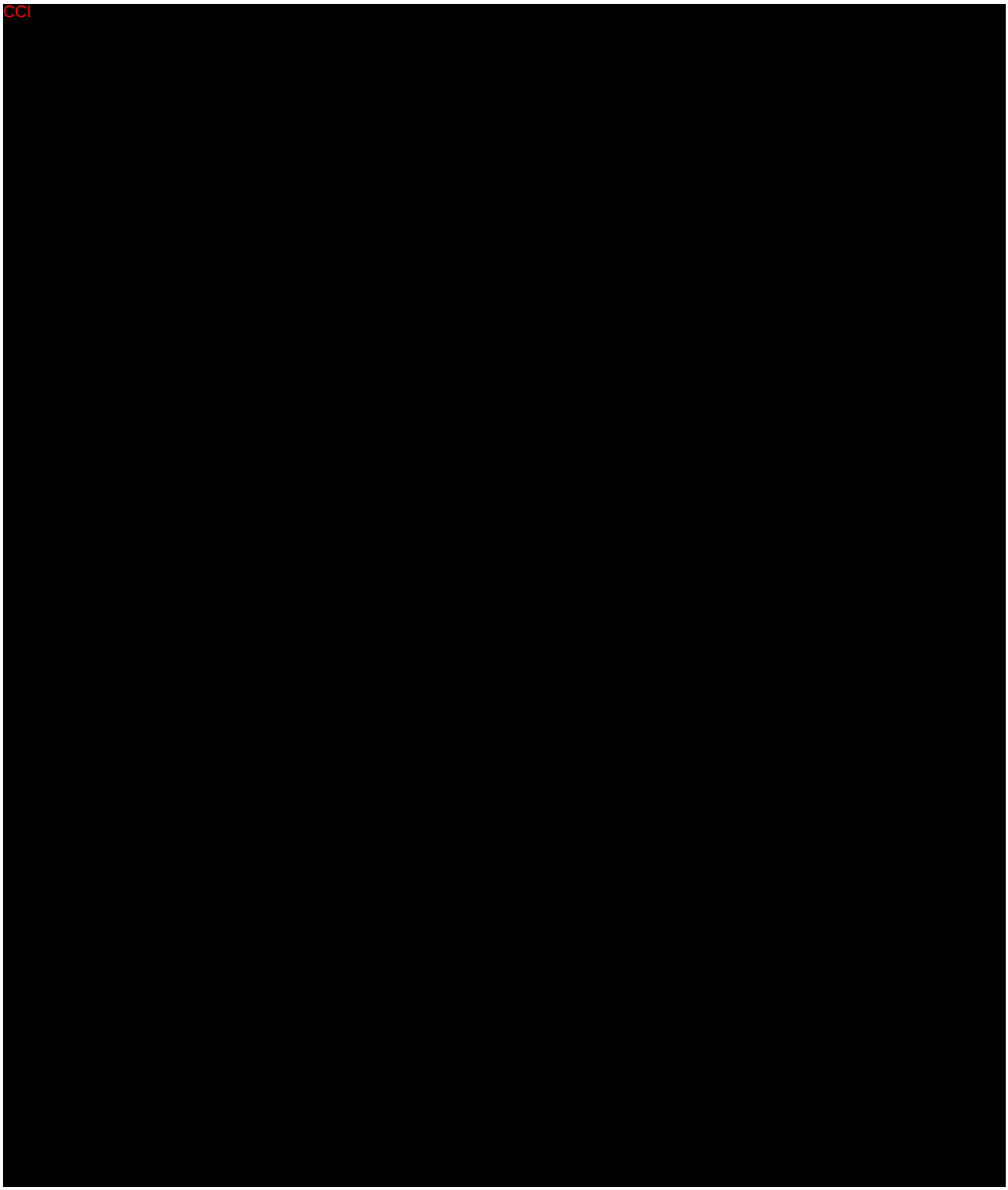

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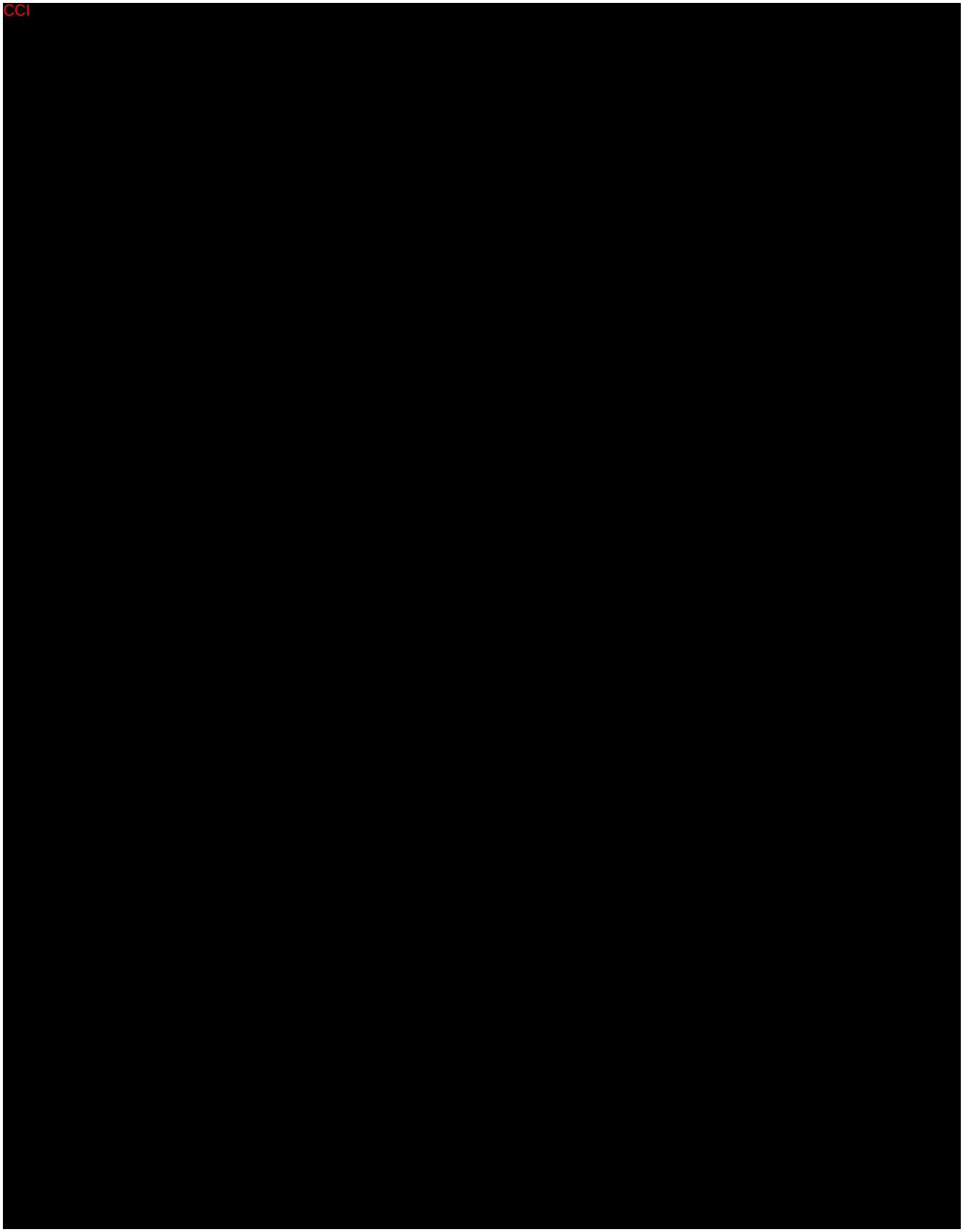

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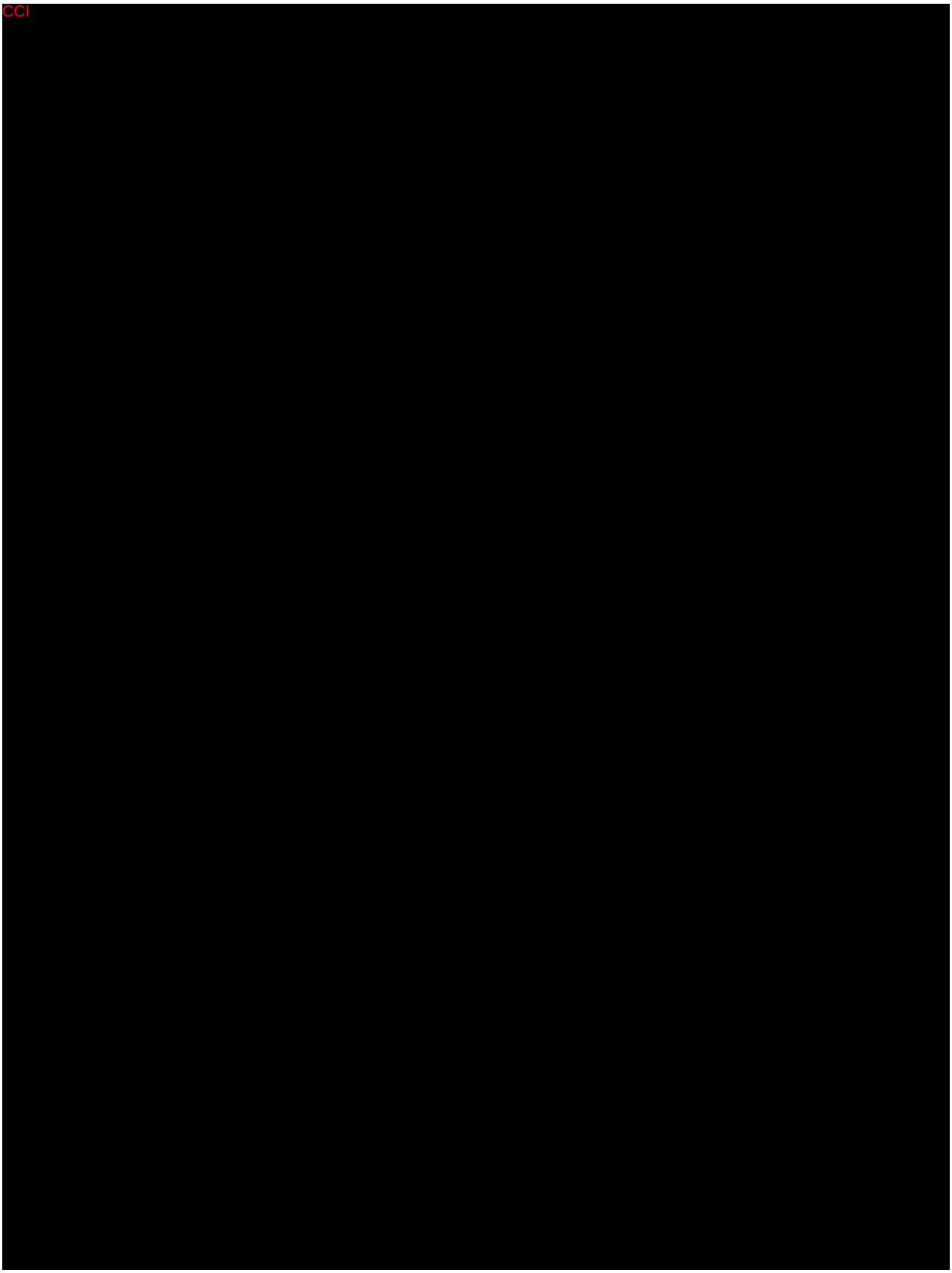

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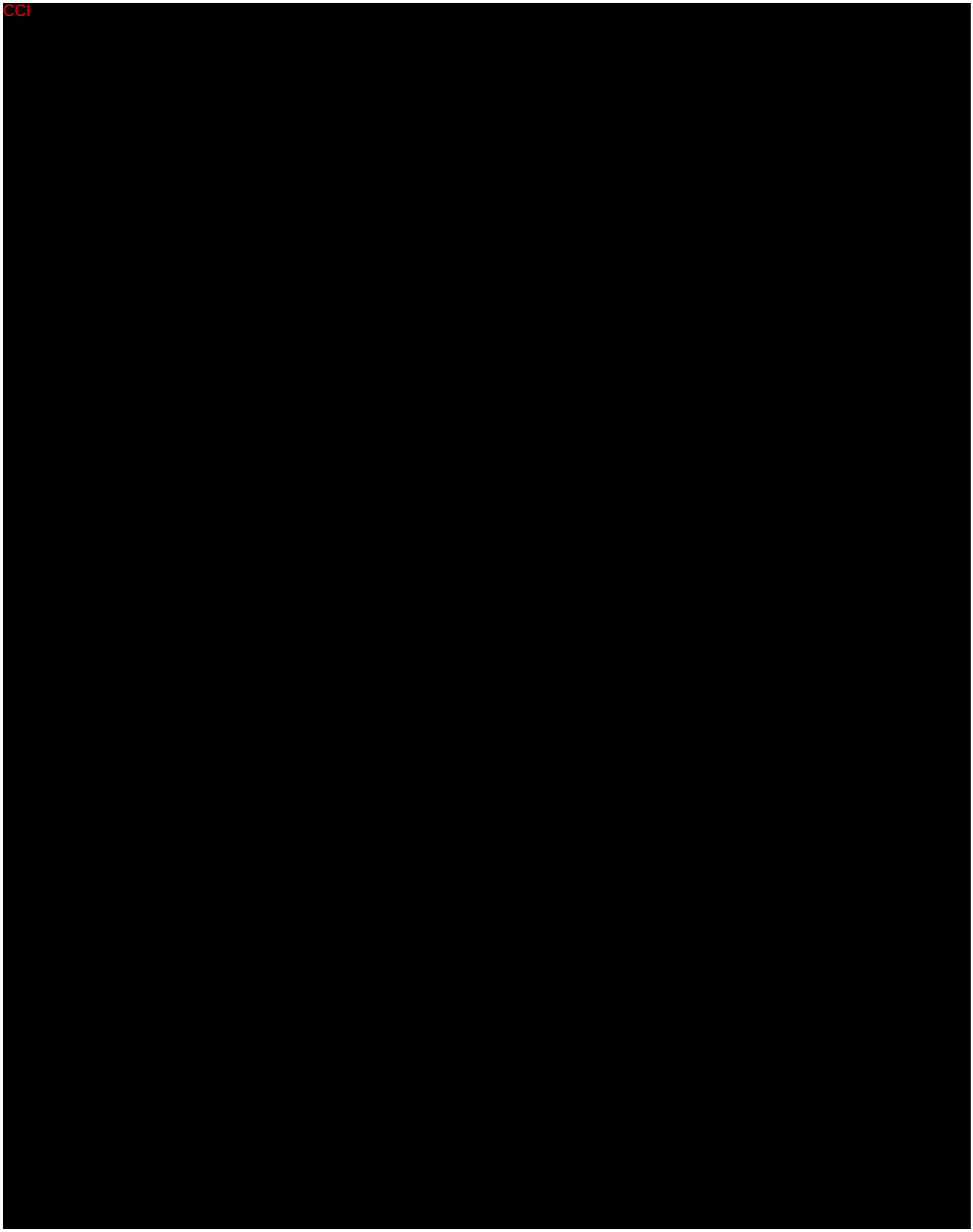

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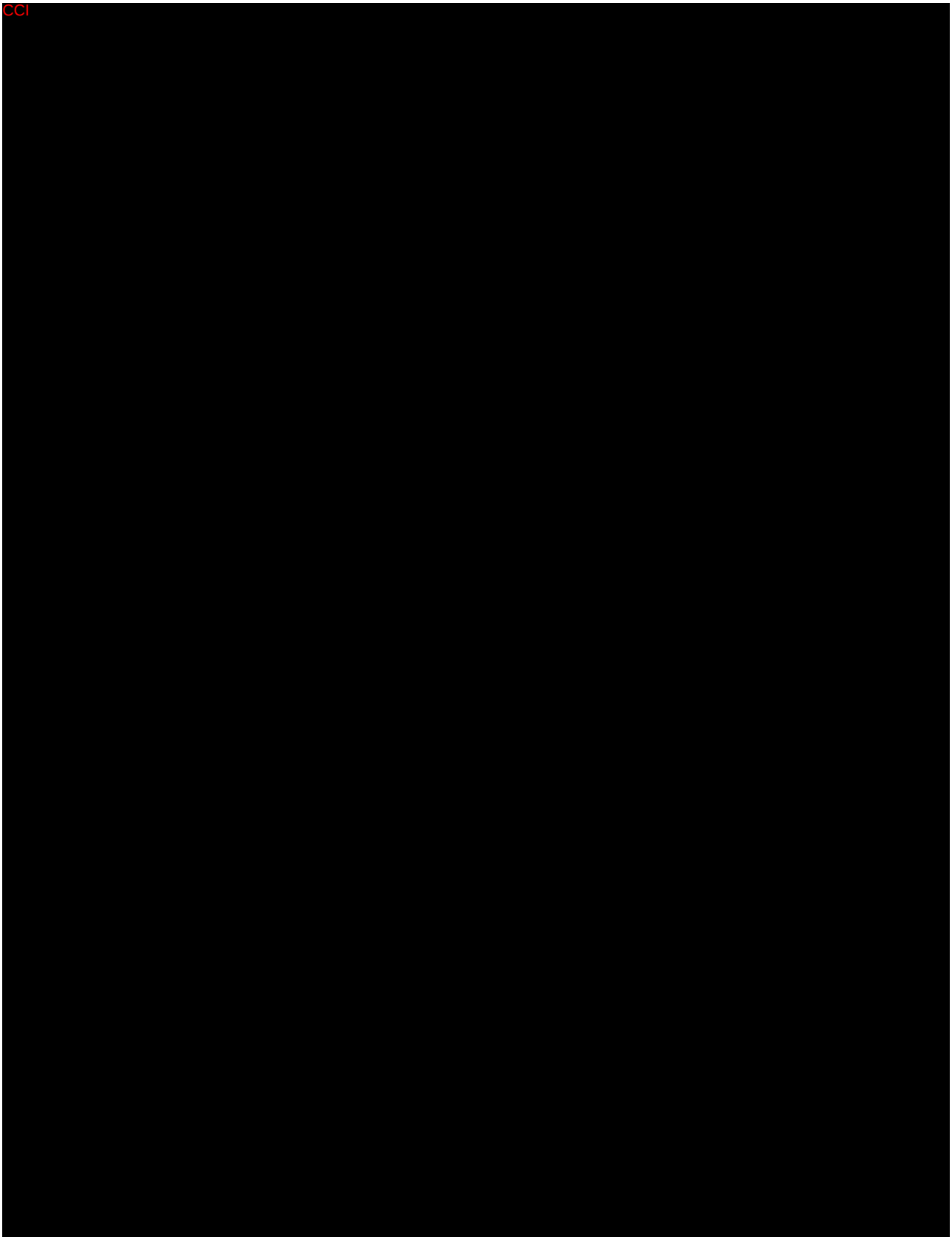

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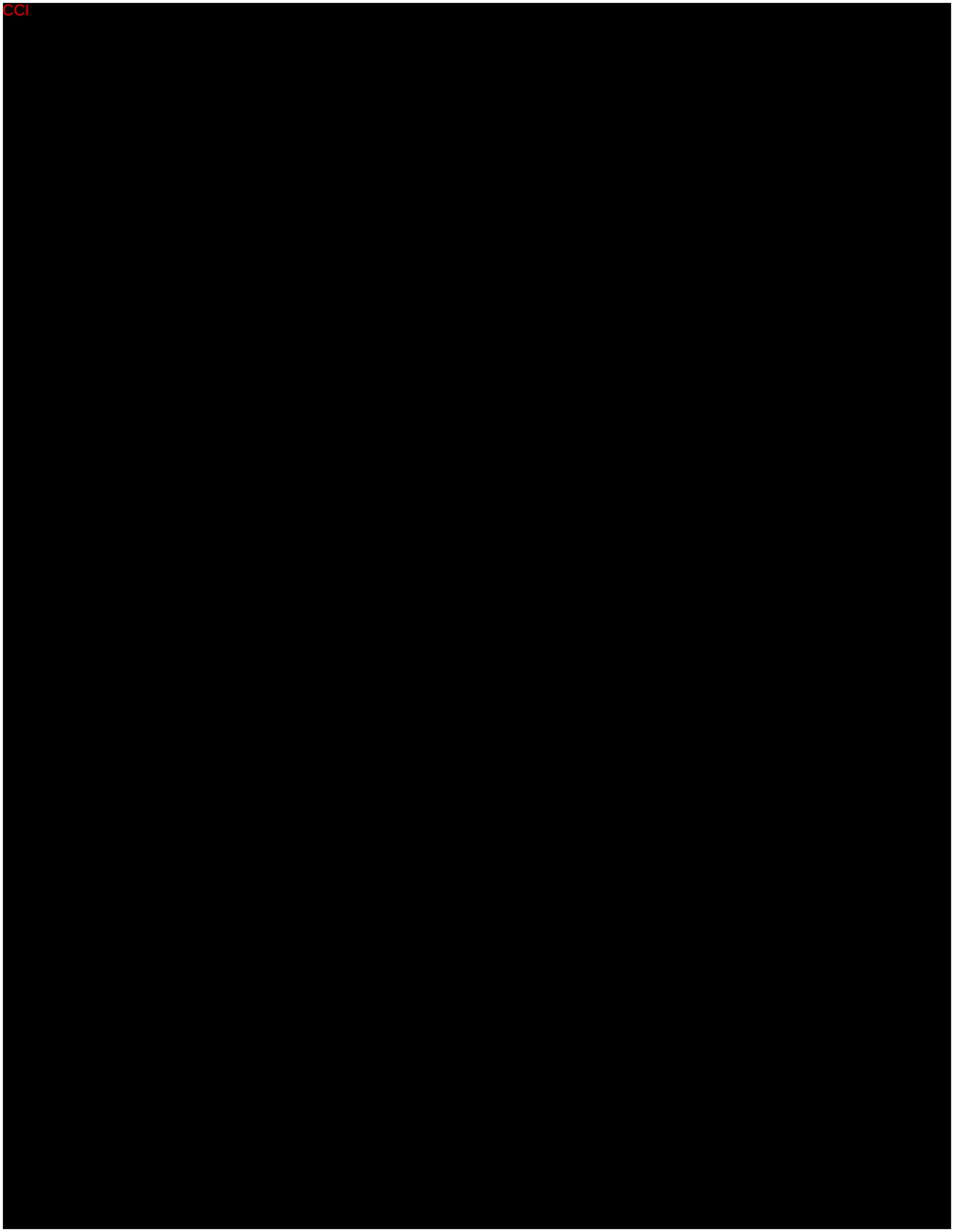

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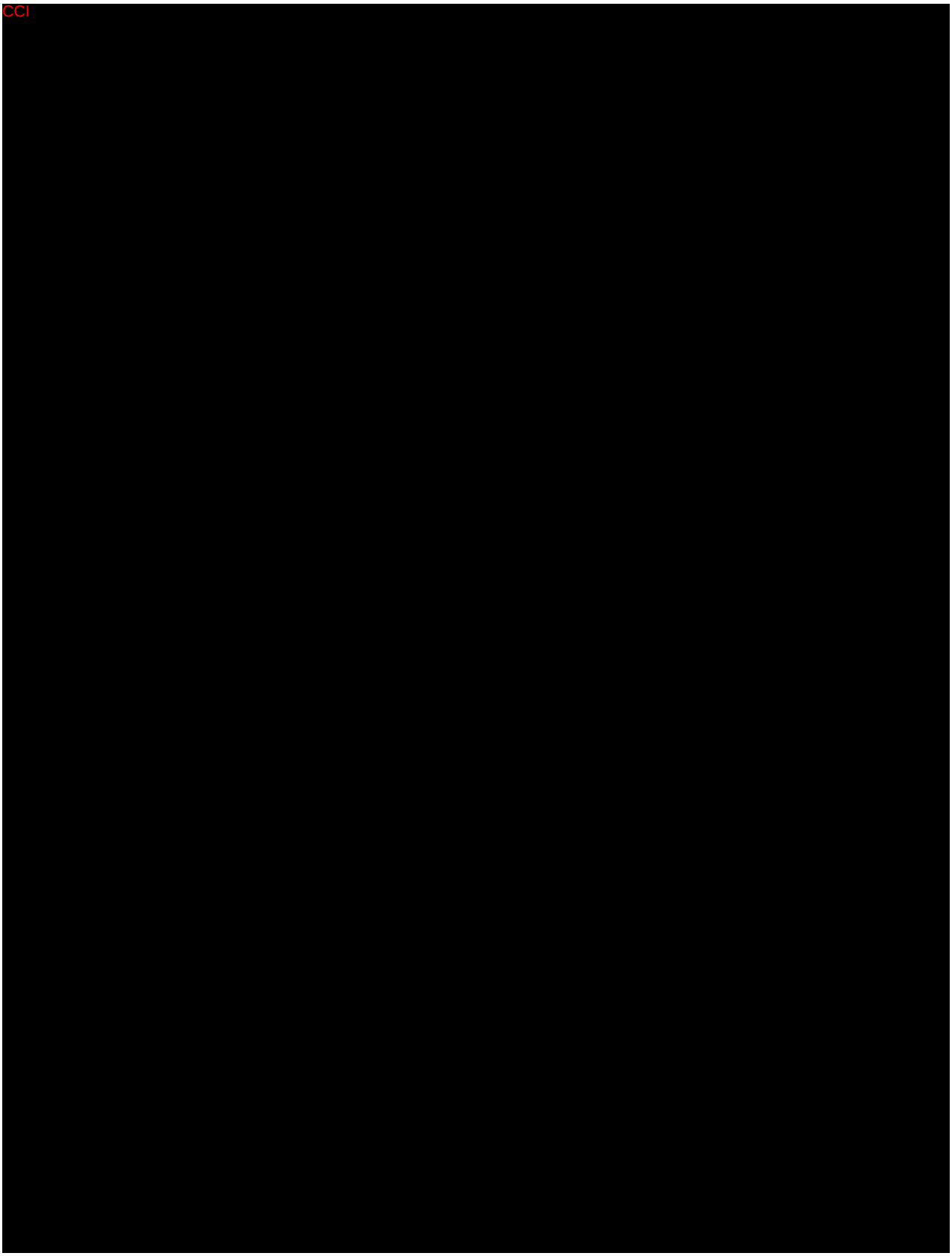

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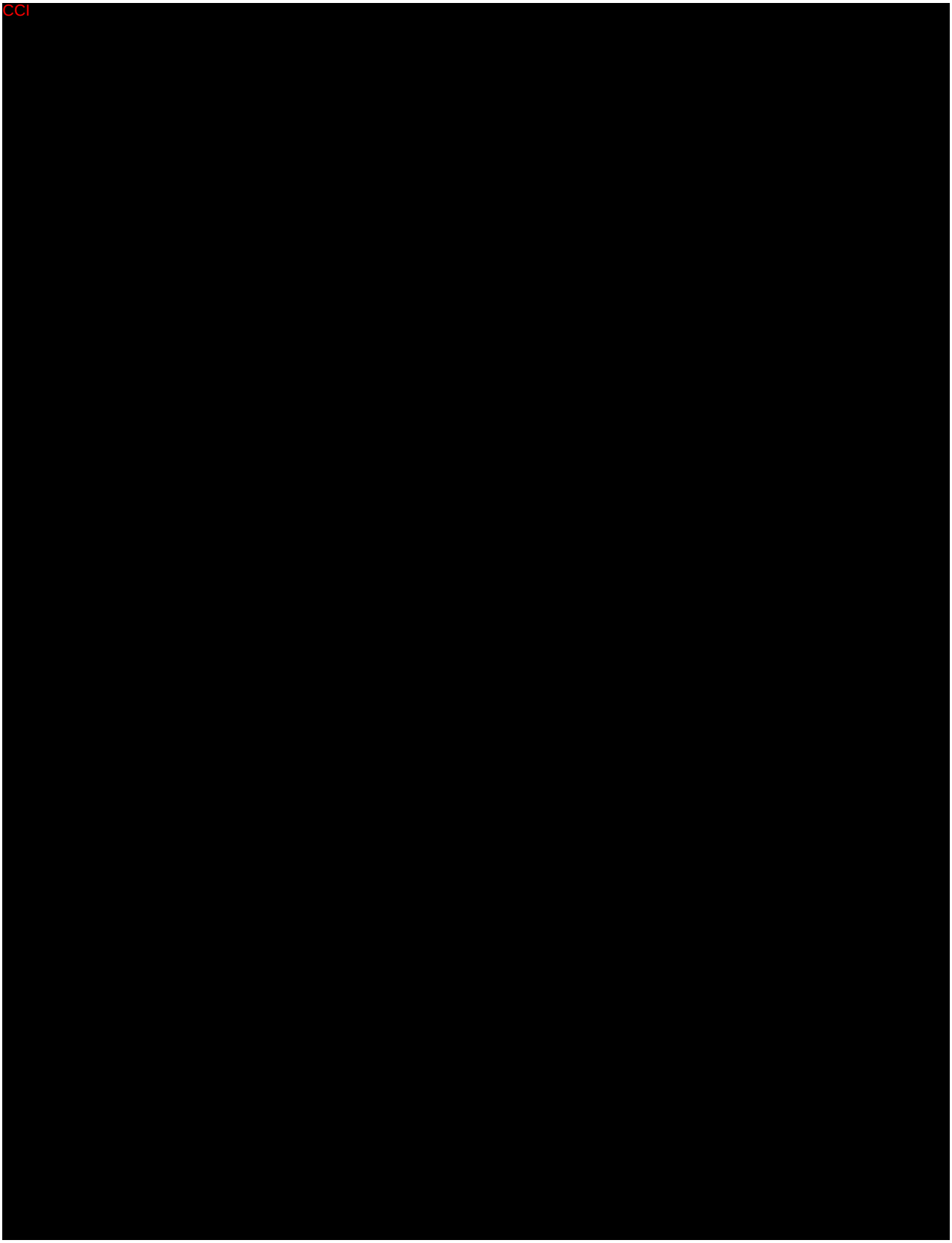

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