CoLab Network

Health Technology Review

Utilization Analysis of Tofacitinib and Other Drugs in Ulcerative Colitis

Phase 1 Scientific Protocol

This observational study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) through the Post-Market Drug Evaluation CoLab Network.

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Abbreviations

CNODES	Canadian Network for Observational Drug Effect Studies
IBD	inflammatory bowel disease
JAK	Janus kinase
MACE	major adverse cardiovascular events
RA	rheumatoid arthritis
TNF	tumour necrosis factor
UC	ulcerative colitis

Amendments and Updates

Table 1: Protocol Version Tracking

Section	Amendment	Rationale
UC base cohort	Exclusion criteria 1 and 3 reordered and specified that the lookback period for exclusion 4 can be before 2010 if data are available.	Edits made during the implementation of analyses. Exclusion criteria 3 (missing data) to be applied before exclusion criteria 1 (age younger than 18 years). Use of additional data for exclusion 4 if applicable.
UC treatment cohorts	Individuals were permitted to enter more than 1 cohort but were excluded if they initiated therapies from multiple categories on the same date.	Additional exclusion applied as this is a feasibility analysis.
Follow-up	Edits made to clarify this section.	Edits made during the implementation of analyses to clarify how to implement this section.
Appendices 3 **and** 5	Edits made to clarify this section.	Edits made during the implementation of analyses to clarify how to implement this section.

Abstract

A retrospective cohort study will be conducted using administrative health databases from 4 Canadian provinces (British Columbia, Manitoba, Ontario, and Saskatchewan), the UK, and the US to describe the use of tofacitinib and other therapies among individuals diagnosed with ulcerative colitis (UC) and to determine the feasibility of a comparative safety study of major adverse cardiac events (MACE), thrombotic events, and cancer using these databases.

Background and Rationale

What Is Known About the Condition

Inflammatory bowel disease (IBD) is an important chronic autoimmune condition that includes UC and Crohn disease. IBD affects nearly 1% of Canadians,[1-3] and UC affects 19.2 per 100,000 Canadians.[2,3]

What Is Known About the Exposure of Interest

Tofacitinib is a Janus kinase (JAK) inhibitor approved by Health Canada in 2018 for moderate to severe UC. The recommended dosage for individuals with UC is initially 10 mg twice daily for at least 8 weeks, and then 5 mg twice daily for maintenance therapy.[4] The 2019 CADTH Reimbursement Review recommended tofacitinib be reimbursed in individuals with moderate to severe UC and "an inadequate response, loss of response or intolerance to either conventional UC therapy or a TNFα [tumour necrosis factor alpha] inhibitor," dependent on additional conditions.[5]

Gaps in Knowledge

Optimal sequencing of advanced therapies (i.e., biologic immunomodulators and JAK inhibitors) in conditions such as UC is an important topic given there are studies that have reported increased risk for MACE, thrombotic events, and malignancy in other populations (such as rheumatoid arthritis).[6-9] Because of these safety signals, a "Serious Warnings and Precautions" box was added to the product monograph of tofacitinib products sold in Canada.[4] However, information on the safety of tofacitinib in individuals with UC, especially from Canadian studies, is sparse.[10-12] Canadian safety data on tofacitinib in individuals with UC is needed to inform formulary policies around the optimal sequencing of advanced therapies and to ascertain whether Health Canada warnings are justified for the UC indication.

What Is the Expected Contribution of This Study?

To address knowledge gaps on the safety of tofacitinib in the younger, potentially healthier population with UC compared with a population with rheumatoid arthritis, the Canadian Network for Observational Drug Effect Studies (CNODES) will conduct a phase 1 descriptive assessment of the real-world rates of MACE, thrombotic events, and cancer in individuals diagnosed with UC who have and have not been exposed to tofacitinib.

Policy Question

What is the safety of tofacitinib in patients with UC?

Policy Impact

Although tofacitinib demonstrates efficacy in patients with moderate to severe UC, new safety signals have emerged resulting in labelling recommendations by the FDA and Health Canada. Patients with rheumatoid arthritis in the studies with the safety signals were older adults with comorbidities and/or at risk for bleeding. Further analyses of the safety of JAK inhibitors (tofacitinib) are needed in the patient population with UC to determine if the safety concerns are the same for patients with UC, who tend to be a younger cohort of patients than those with rheumatoid arthritis. These findings will have an impact on formulary management in the future, given that tofacitinib has lost its exclusivity, and generic versions are becoming available. Additionally, there is a substantial pipeline of new and emerging drugs for the treatment of adults with moderate to severe UC, which include multiple JAK inhibitors in phase II/III of clinical development. Earlier use of JAK inhibitors at generic pricing may provide better patient outcomes with budgetary savings. The main opposition to earlier use of JAKs is their safety profile, which this study will look to address in the population with UC specifically.

Research Question

What is the safety profile (relative to other advanced therapies) of tofacitinib among individuals with UC in terms of MACE, hospitalized thrombotic events, and cancer?

Objectives

In each of 4 UC drug treatment cohorts (tofacitinib cohort, TNF alpha cohort, vedolizumab or ustekinumab cohort, and conventional therapy cohort) we will:

- estimate the crude incidence rate of MACE
- estimate the crude incidence rate of hospitalized thrombotic events
- estimate the crude incidence rate of cancer
- determine the prevalence of use of other treatments for UC before and after starting treatment with tofacitinib.

Research Methods

Study Design

To address these objectives, a retrospective descriptive cohort design will be used. UC drug treatment cohorts will be assembled and analysed using administrative health databases from 4 Canadian provinces (British Columbia, Manitoba, Saskatchewan, and Ontario), the US (Merative MarketScan), and the UK (Clinical Practice Research Datalink [CPRD] Aurum). The drug treatment cohorts will consist of individuals who were diagnosed with UC between January 1, 2010, and March 31, 2023, and were at least 18 years of age at the date of diagnosis. Individuals will be classified into drug treatment cohorts based on initiating treatment(s) between January 1, 2018, and March 31, 2023 (or the latest date of data availability at each site).

Study Population and Setting

At each study side, a UC base cohort will be established. From this base cohort, UC drug treatment cohorts will be created from which the incidence of MACE, hospitalized thrombotic events, and identified cancers will be described.

UC Base Cohort

At each site, **the base cohort of individuals with a diagnosis of UC** will be based on the following criteria.

Inclusion Criteria

- Diagnosed with UC (International Classification of Diseases Ninth Revision [ICD-9]: 556; Tenth Revision [ICD-10]: K51) between January 1, 2010, and March 31, 2023, based on at least 1 record of a

hospitalization or a visit to a physician, emergency department, or ambulatory care provider. The UC case index date will be the earliest date of diagnosis during this period.

Note: we selected a sensitive and nonspecific definition of UC to increase the sample size, with the understanding that the main interest in this study is to estimate the risk in the population with IBD (in contrast to a population with rheumatological diseases). Refer to Appendix 1 for CPRD codes.

Exclusion Criteria

Individuals with UC will be excluded from the base cohort if they:

- are missing data on sex or date of birth
- have less than 2 years of continuous health plan enrolment (1 year in MarketScan) before the index date (cumulative gaps of 90 days or less are permitted; i.e., do not result in exclusion)
- are younger than 18 years of age at their UC index date
- have a diagnosis of 1 or more of the following diseases treated with the advanced therapies used in UC: Crohn disease, ankylosing spondylitis or nonradiographic axial spondyloarthritis; psoriasis; psoriatic arthritis; rheumatoid arthritis, or polyarticular juvenile idiopathic arthritis at any time on or after January 1, 2010, and before or on the UC index date (based on data available in each site or before 2010 if data are available) (refer to Appendix 2).

UC Treatment Cohorts

At each site, we will define 4 UC drug treatment cohorts from within the UC base cohort, as follows:

- **Tofacitinib cohort**: Includes new users of tofacitinib. These are individuals with an index prescription for tofacitinib between January 1, 2018, and March 31, 2023, with a minimum of 2 years without a prior prescription for tofacitinib, and for whom the date of the index prescription for tofacitinib is on or after the UC base cohort index date.
- **TNF alpha cohort**: Includes new users of TNF alpha inhibitor. These are individuals with an index prescription for infliximab, adalimumab, or golimumab between January 1, 2018, and March 31, 2023, with a minimum of 2 years without a prior prescription in this category, and for whom the date of the index prescription in this category is on or after the UC base cohort index date.
- **Vedolizumab or ustekinumab cohort**: Includes new users of vedolizumab, a selective alpha 4 beta7 inhibitor, or ustekinumab, an IL-12/23 p40 inhibitor, alone or in combination with each other. These are individuals with an index prescription for vedolizumab or ustekinumab between January 1, 2018, and March 31, 2023, with a minimum of 2 years without a prior prescription in this category, and for whom the date of the index prescription in this category is on or after the UC base cohort index date.
- **Conventional therapy cohort**: Includes users of a new conventional UC therapy. These are individuals with an index prescription for oral 5-aminosalicylates, corticosteroids, azathioprine, 6-mercaptopurine, or cyclosporine between January 1, 2018, and March 31, 2023, with a minimum of 2 years without a prior prescription in this category, and for whom the date of the index prescription in this category is on or after the UC base cohort index date.

A list of medications for the tofacitinib, TNF alpha, and vedolizumab or ustekinumab cohorts is included in Appendix 3. A list of medications for the conventional therapy cohort is included in Appendix 4.

For each cohort, a cohort entry date will be defined as the earliest date of initiating a drug in the category between January 1, 2018, and March 31, 2023 (or until the latest data available). Individuals can enter more than 1 treatment cohort, but individuals eligible for multiple treatment cohorts on the same date will be excluded.

Exclusion Criteria for UC Treatment Cohorts

- Individuals who lost enrolment (for any reason, including death) in their health plan before cohort entry, defined as a 90-day gap or longer in enrolment within 2 years before the cohort entry date.
- Individuals with a diagnosis of ankylosing spondylitis or nonradiographic axial spondyloarthritis; psoriasis; psoriatic arthritis; Crohn disease; or rheumatoid arthritis or polyarticular juvenile idiopathic arthritis between the index date and cohort entry (inclusive) (refer to Appendix 2).

Follow-Up Criteria

Follow-up time is defined in this section. Cancer outcomes will require minimum follow-up (MFUP) time intervals due to delayed outcome eligibility. The MFUP is defined as the interval immediately following treatment cohort entry during which person-time is not accrued based on the assumption that outcomes that occur within this interval cannot be caused by the exposure (i.e., induction period). MFUP will be defined as follows:

- For all noncancer outcomes, the MFUP is 0 days.
- For nonmelanoma skin cancer outcome, the MFUP is 180 days.
- For lymphoma, lung cancer, and other cancer outcomes, the MFUP is 90 days.

For each treatment cohort and outcome, individuals will contribute follow-up time from the day after the MFUP end date until the earliest of the following events:

- The event
- March 31, 2023 (or the latest date of data availability at each site)
- Loss of enrolment in the health plan (including death), defined as 90 days gap in enrolment or longer; individuals will be censored at the last date of enrolment

  Notes:

  - For the MACE composite outcome, cardiovascular death is 1 component of the outcome. If enrolment was lost due to death, check for cardiovascular death before censoring.
  - For nonmelanoma skin cancer outcome, a minimum of 180 days of follow-up is required for each individual. If a site has data until March 31, 2023, nonmelanoma skin cancer follow-up will be censored on October 2, 2022. If an individual left the province (or the MarketScan or CPRD databases) on March 15, 2023, nonmelanoma skin cancer follow-up will be censored on September 16, 2022.

    - For other cancer outcomes (i.e., cancer excluding nonmelanoma skin cancer, lymphoma, and lung cancer) a minimum of 90 days of follow-up is required. If a site has data until March 31, 2023, cancer follow-up will be censored on December 31, 2022. If an individual left the province (or the MarketScan or CPRD databases) on March 15, 2023, cancer follow-up will be censored on December 16, 2022.
    - Each site will check the availability of all data sources and will apply the same censoring criteria (follow-up criteria 1 and 2) if data are missing for the outcome. For example, if hospital data are available only until March 31, 2022, then individuals will be censored at that date for the MACE and thrombotic outcome.
- Death
- Switching to or between the 3 advanced UC treatment cohorts (refer to Appendix 3 for a list of advanced UC treatments) or discontinuation of advanced treatment cohort eligibility; the discontinuation date will be the date corresponding to the end of supply for advanced treatments (Appendix 3) plus 60 days

  Notes:

    - Allow 60 days grace period following the end of supply of the last prescription of the study drug.
    - For infliximab, we will impute a minimum supply of 42 days (i.e., if recorded supply is for less than 42 days, we will impute it to 42 days for the purpose of identifying discontinuation).
    - For golimumab, we will impute a minimum supply of 28 days (i.e., if recorded supply is for less than 28 days, we will impute it to 28 days for the purpose of identifying discontinuation).
    - For vedolizumab and/or ustekinumab, we will impute a minimum supply of 56 days (i.e., if recorded supply is for less than 56 days, we will impute it to 56 days for the purpose of identifying discontinuation).

Study Variables

Outcomes

- MACE will be defined as a composite outcome previously used in a CNODES study.[13] It consists of 1 of the following:
    - cardiovascular death (using the algorithm previously validated by CNODES investigators[14])
    - hospitalization with a diagnosis for myocardial infarction
    - hospitalization with a diagnosis for ischemic stroke.
- Hospitalization for a thrombotic event will be defined as a composite outcome consisting of 1 of the following:
    - arterial thrombotic events as has previously been used by CNODES investigators[15]
    - venous thrombotic events (deep vein thrombosis and pulmonary embolus).
- Cancer will be analysed separately for the following 4 outcomes:

- any cancer, excluding nonmelanoma skin cancer[6,7]
- nonmelanoma skin cancer[7] will be defined as a composite outcome previously used by CNODES investigators,[16] including all of the following:
  - the presence of a diagnosis code
  - the presence of an inpatient or outpatient procedure code or associated physician service fee code within ± 180 days of the previous diagnosis code.
- lymphoma
- lung cancer.[7]

Algorithms to identify the study outcomes are included in Appendix 5 and Appendix 6.

Data Analysis

Statistical Analysis Plan

Descriptive information on the UC base cohort and UC treatment cohorts, including demographic, follow-up times, and event counts, will be reported by each site, subject to small cell restrictions. For each site, the period prevalence of diagnosed UC (January 1, 2010, to March 31, 2023) will be calculated, as will crude cumulative incidence proportions and crude incidence rates for each outcome.

Meta-Analysis

Results will be reported separately for each site (i.e., results will not be meta-analysed or aggregated across sites).

Data Sources

We will use administrative health databases from 4 Canadian provinces (British Columbia, Manitoba, Saskatchewan, and Ontario), the US (Merative MarketScan), and the UK (Clinical Practice Research Datalink – CPRD Aurum). These databases contain records of physician encounters, emergency department visits, and hospitalizations, which include the diagnostic information required to identify individuals with UC and their comorbid conditions. The databases also contain prescription records, which will be used to determine UC treatment cohorts and patterns of UC treatment, and demographic information, which will be used to determine age and sex. The US MarketScan database includes more than 70 million individuals covered by large US employer health insurance plans and government and public organizations. The CPRD Aurum[17] is a primary care database that contains the records of 40 million individuals (including 14 million individuals currently registered) from 1,370 general practices in the UK. The CPRD database will be linked to the Hospital Episode Statistics database, which contains hospital admission information. Linkage with the Hospital Episode Statistics is available for approximately 90% of the participating practices in CPRD.

Limitations

Our study design has important limitations. First, our definition of UC is based on 1 record of a health care encounter and is therefore sensitive rather than specific. This approach was taken to increase sample size,

with the understanding that the main intent of the query is to conduct a feasibility analysis to estimate risk of the identified outcome in a population with UC in contrast to a population with rheumatological disease. Second, the proposed analyses are crude, without adjustment for individual characteristics that may confound the association between study therapies and the safety outcomes. Third, the lag period to be used for the cancer outcomes is shorter than typically used in observational studies of drug and cancer outcomes,[18] as a more ideal, longer lag period is not feasible given the timing of coverage of tofacitinib for UC and the limited follow-up time available to us. Fourth, our case definition for cancer for this feasibility analysis may be imprecise, which may result in overestimation of the number of events. Lastly, our study is limited to data from select Canadian provinces, the UK, and the US, and findings may not be generalizable to other jurisdictions.

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Appendix 1: CPRD READ Codes for Ulcerative Colitis

Note that this appendix has not been copy-edited.

UC READ Codes[19]

J41...12

J410.00

J410000

J410100

J410200

J410300

J410400

J410z00

J411.00

J412.00

Jyu4100

N031000

N045400

J08z900

Appendix 2: Other Diseases Treated With Advanced Therapies for Ulcerative Colitis

Note that this appendix has not been copy-edited.

Table 2: Other Diseases Treated With Advanced Therapies for Ulcerative Colitis

Disease	Description	ICD-9 codes	ICD-10 codes
Ankylosing spondylitis and nonradiographic axial spondyloarthritis	One health care encounter (outpatient, hospitalization [any diagnostic position], emergency department) For UC base cohort: at anytime on or after January 1, 2010, and before/on the UC index date (and based on data available in each site) For UC treatment cohorts: between the index date and cohort entry (inclusive)	720.xx	M45.x
Crohn disease	One health care encounter For UC base cohort: On or after January 1, 2010, and before/on the UC index date (and based on data available in each site) For UC treatment cohorts: between the index date and cohort entry (inclusive)	555.x	K50.x
Psoriasis	One health care encounter For UC base cohort: On or after January 1, 2010, and before/on the UC index date (and based on data available in each site) For UC treatment cohorts: between the index date and cohort entry (inclusive)	696.x	L40.x, excluding L40.5x
Psoriatic arthritis	One health care encounter in the 3 months before prescription For UC base cohort: On or after January 1, 2010, and before/on the UC index date (and based on data available in each site) For UC treatment cohorts: between the index date and cohort entry (inclusive)	696.0	L40.5x
Rheumatoid arthritis and polyarticular juvenile idiopathic arthritis	One health care encounter For UC base cohort: On or after January 1, 2010, and before/on the UC index date (and based on data available in each site) For UC treatment cohorts: between the index date and cohort entry (inclusive)	714.x	M05.x, M06.x, M08.x, excluding M08.1x

Appendix 3: Advanced Therapies for Ulcerative Colitis

Note that this appendix has not been copy-edited.

Table 3: Advanced Therapies for Ulcerative Colitis

Therapeutic group	Generic name	ATC codes
JAK inhibitor	Tofacitinib	L04AA29
TNF alpha inhibitors (originators and biosimilars)	Adalimumab	L04AB04
	Infliximab	L04AB02
	Golimumab	L04AB06
Interleukin-12/23 inhibitor	Ustekinumab	L04AC05
Integrin blocker	Vedolizumab	L04AA33

ATC = Anatomical Therapeutic Chemical; JAK = Janus kinase; TNF = tumour necrosis factor.

Note: Advanced therapies indicated for ulcerative colitis in Canada are listed.

Appendix 4: Conventional Therapies for Ulcerative Colitis

Note that this appendix has not been copy-edited.

Table 4: Conventional Therapies for Ulcerative Colitis

Therapeutic group	ATC codes
5-ASA compounds	
Sulfasalazine	A07EC01
Mesalazine	A07EC02
Olsalazine	A07EC03
Balsalazide	A07EC04
Corticosteroids	
Prednisone	A07EA03, H02AB07
Prednisolone	A07EA01, H02AB06
Hydrocortisone	A07EA02, H02AB09
Methylprednisolone	H02AB04
Budesonide	A07EA06
Immunomodulators	
Azathioprine	L04AX01
Methotrexate	L04AX03
6-Mercaptopurine	L01BB02
Cyclosporine (ciclosporin)	L04AD01

ATC = Anatomical Therapeutic Chemical.

Appendix 5: Study Outcomes

Note that this appendix has not been copy-edited.

Table 5: Study Outcomes

Condition	Diagnosis or procedure codes	Data source and definition	Comment
MACE			
Myocardial infarction[13]	ICD-10 code: I21.x	Hospitalization (outcome date is admission date)	Primary position/most responsible diagnosis (type M)
Ischemic stroke[13]	ICD-10 codes: I63.x, I64.x	Hospitalization (outcome date is admission date)	Primary position/most responsible diagnosis (type M)
Cardiovascular mortality[14]	In-hospital death with a primary cardiovascular diagnosis [ICD-10 codes: I00.x-I77.x (except I46.9)] recorded as primary position/most responsible diagnosis (type M); OR Out-of-hospital death (including death in the emergency department if data available) without: • Documentation of cancer (ICD-9 codes: 140-172, 174-209; ICD-10-CA: C00-C43, C45-C97) in hospital, emergency department or physician claims data in the prior year; or • Documentation of trauma (ICD-9 codes: 800-999, E000-E999; ICD-10-CA: S00-T98, V01-Y98) in hospital, emergency department or physician claims data in the preceding month.		
Thrombotic events			
Arterial thromboembolism[15] (including ischemic stroke or systemic embolization)	ICD-10 codes: I63.x, I64.x, I74.x	Hospitalization (outcome date is admission date)	Primary position/most responsible diagnosis (type M)
Venous thromboembolism (including deep vein thrombosis and pulmonary embolism)	ICD-10 codes: I26.x; I80.x; I81.x; I82.x	Hospitalization (outcome date is admission date)	Primary position/most responsible diagnosis (type M)
Cancer			
Cancer (excluding nonmelanoma skin cancer)	Diagnosis codes: ICD-9 codes: 140.x-172.x; 174.x-209.x ICD-10 codes: C00.x-C43.x; C45.x-C97.x Procedure codes: 1. Ambulatory codes for radiotherapy and chemotherapy (as applicable in each site) 2. CCI codes in hospital records: 1.xx.35.xx (chemotherapy); 1.xx.27.xx (radiotherapy) 3. Hospital or emergency	One hospitalization with a diagnosis code (outcome date is admission date) OR 2 visits to physicians/ nurse practitioners within 3 months with diagnosis codes (outcome date is second diagnosis date) OR One record (outpatient or in-hospital) with a procedure code (outcome date is admission date)	Any diagnostic position

Condition	Diagnosis or procedure codes	Data source and definition	Comment
	department types or MRDx/main problem: Z51.0, Z51.1		
Nonmelanoma skin cancer[16]	Diagnosis codes: ICD-9 codes: 173.xx ICD-10 codes: C44.xx and procedure codes on diagnosis date or the 180 days before/after the diagnosis	Hospitalization (outcome date is admission date) Visits to physicians/nurse practitioners (outcome date is the latest among diagnosis/procedure date)	Refer to Appendix 6: Procedure codes to identify nonmelanoma skin cancer
Lymphoma	Diagnosis codes: ICD-9: 200.x, 202.x, 204.x ICD-10: C81.x-C86.x	Has the cancer outcome plus at least 1 lymphoma diagnosis code in hospitalization, emergency department, or a visit to physicians/nurse practitioners, on or after the first cancer encounter (outcome date is the lymphoma diagnosis date)	Any diagnostic position: hospitalization, emergency department, visits to physicians/nurse practitioners
Lung cancer	ICD-9 codes: 162.x ICD-10 codes: C34.x	Meets the definition for the "Cancer (excluding non-melanoma skin cancer)" plus at least 1 diagnosis code for lung cancer in hospitalization, emergency department, or a visit to physicians/nurse practitioners, on or after the first cancer encounter (outcome date is the lung cancer diagnosis date)	Any diagnostic position: hospitalization, emergency department, visits to physicians/nurse practitioners

CCI = Canadian Classification of Health Interventions; ICD = International Classification of Diseases; MRDx = most responsible diagnosis (for the individual's stay in hospital).

Appendix 6: Procedure Codes for Nonmelanoma Skin Cancer

Note that this appendix has not been copy-edited.

Table 6: Procedure Codes for Nonmelanoma Skin Cancer

Code	Description
International Classification of Diseases Version 9 (ICD-9)[16]	
08.11	Biopsy of eyelid
08.2x	Removal of lesion of eyelid
18.12	Biopsy of external ear
18.29	Excision or destruction of other lesion of external ear
18.31	Radical excision of lesion of external ear
21.22	Biopsy of nose
21.3x	Local excision or destruction of lesion of nose
27.23	Biopsy of lip
27.42	Wide excision of lesion of lip
27.43	Other excision of lesion or tissue of lip
86.11	Closed biopsy of skin and subcutaneous tissue
86.24	Chemosurgery of skin
86.3	Other local excision or destruction of lesion or tissue of skin and subcutaneous tissue
86.4	Radical excision of skin lesion
Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP)[16]	
22.1	Excision of lesion or tissue of eyelid
22.13	Other excision of single lesion of eyelid
22.14	Excision of multiple lesions of eyelids
22.81	Biopsy of eyelid
30.1	Excision or destruction of lesion of external ear
30.19	Excision or destruction of other lesion of external ear
30.21	Radical excision of lesion of external ear
30.81	Biopsy of external ear
33.2	Excision or destruction of lesion of nose
33.21	Excision of lesion of nose, unqualified
33.23	Local excision or destruction of other lesion of nose
33.81	Biopsy of nose
98.1	Excision of skin and subcutaneous tissue
98.12	Local excision or destruction of lesion or tissue of skin and subcutaneous tissue

Code	Description
98.13	Radical excision of skin lesion
98.81	Biopsy of skin and subcutaneous tissue
Canadian Classification of Health Interventions (CCI)[16]	
1.YC.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of ear
1.YS.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of abdomen and trunk NEC
1.YT.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of arm
1.YR.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of axillary region
1.YF.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of face NEC
1.YW.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of foot
1.YB.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of forehead
1.YU.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of hand
1.YV.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of leg
1.YE.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of lip
1.YG.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of neck
1.YD.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of nose
1.YZ.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of abdomen/trunk and extremities
1.YA.87.^^	Excision (partial, total, radical, with/without repair or reconstruction) of skin of scalp
1CX87UD	Excision partial, eyelid NEC no tissue used (for repair)using full thickness excision of lesion (more than one fourth of lid margin)
1CX87UDXXA	Excision partial, eyelid NEC with autograft full thickness excision of lesion (more than one fourth of lid margin)
1CX87UDXXK	Excision partial, eyelid NEC with homograft [e.g., amniotic membrane transplant (AMT) or graft] full thickness excision of lesion (more than one fourth of lid margin)
1CX87VPXXA	Excision partial, eyelid NEC with autograft partial thickness excision of lesion (up to one fourth of lid margin)
1CX87VPXXK	Excision partial, eyelid NEC with homograft [e.g., amniotic membrane transplant (AMT) or graft] partial thickness excision of lesion (up to one fourth of lid margin)
1CX88UDXXA	Excision, partial, with reconstruction, eyelid NEC with autograft [e.g., hair follicles], full thickness excision of major lesion (more than one fourth of lid margin)
1CX88UDXXC	Excision, partial, with reconstruction, eyelid NEC with composite graft [e.g., hair follicle], full thickness excision of major lesion (more than one fourth of lid margin)
1CX88UDXXE	Excision, partial, with reconstruction, eyelid NEC with local flap, full thickness excision of major lesion (more than one fourth of lid margin)
1CX88UDXXF	Excision, partial, with reconstruction, eyelid NEC with free flap, full thickness excision of major lesion (more than one fourth of lid margin)
1CX88UDXXK	Excision, partial, with reconstruction, eyelid NEC with homograft [e.g., amniotic membrane transplant (AMT) or graft], full thickness excision of major lesion (more than one fourth of lid margin)
1CX88UDXXQ	Excision, partial, with reconstruction, eyelid NEC with combined types of flaps and grafts, full thickness excision of major lesion (more than one fourth of lid margin)

Code	Description
1CX88VPXXA	Excision, partial, with reconstruction, eyelid NEC with autograft [e.g., hair follicles], partial thickness excision of major lesion (up to one fourth of lid margin)
1CX88VPXXC	Excision, partial, with reconstruction, eyelid NEC with composite graft [e.g., hair follicle], partial thickness excision of major lesion (up to one fourth of lid margin)
1CX88VPXXE	Excision, partial, with reconstruction, eyelid NEC with local flap, partial thickness excision of major lesion (up to one fourth of lid margin)
1CX88VPXXF	Excision, partial, with reconstruction, eyelid NEC with free flap, partial thickness excision of major lesion (up to one fourth of lid margin)
1CX88VPXXK	Excision, partial, with reconstruction, eyelid NEC with homograft [e.g., amniotic membrane transplant (AMT) or graft], partial thickness excision of major lesion (up to one fourth of lid margin)
1CX88VPXXQ	Excision, partial, with reconstruction, eyelid NEC with combined types of flaps and grafts, partial thickness excision of major lesion (up to one fourth of lid margin)
Current Procedural Terminology (CPT)[20]	
11600	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter 0.5 cm or less
11601	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter 0.6 to 1.0 cm
11602	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter 1.1 to 2.0 cm
11603	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter 2.1 to 3.0 cm
11604	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter 3.1 to 4.0 cm
11606	Excision, malignant lesion including margins, trunk, arms, or legs; excised diameter over 4.0 cm
11620	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 0.5 cm or less
11621	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 0.6 to 1.0 cm
11622	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 1.1 to 2.0 cm
11623	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 2.1 to 3.0 cm
11624	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter 3.1 to 4.0 cm
11626	Excision, malignant lesion including margins, scalp, neck, hands, feet, genitalia; excised diameter over 4.0 cm
11640	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 0.5 cm or less
11641	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 0.6 to 1.0 cm
11642	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 1.1 to 2.0 cm
11643	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 2.1 to 3.0 cm
11644	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter 3.1 to 4.0 cm
11646	Excision, malignant lesion including margins, face, ears, eyelids, nose, lips; excised diameter over 4.0 cm
17260	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), trunk, arms or legs; lesion diameter 0.5 cm or less
17261	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), trunk, arms or legs; lesion diameter 0.6 to 1.0 cm
17262	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), trunk, arms or legs; lesion diameter 1.1 to 2.0 cm

Code	Description
17263	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), trunk, arms or legs; lesion diameter 2.1 to 3.0 cm
17264	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), trunk, arms or legs; lesion diameter 3.1 to 4.0 cm
17266	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), trunk, arms or legs; lesion diameter over 4.0 cm
17270	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), scalp, neck, hands, feet, genitalia; lesion diameter 0.5 cm or less
17271	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), scalp, neck, hands, feet, genitalia; lesion diameter 0.6 to 1.0 cm
17272	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), scalp, neck, hands, feet, genitalia; lesion diameter 1.1 to 2.0 cm
17273	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), scalp, neck, hands, feet, genitalia; lesion diameter 2.1 to 3.0 cm
17274	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), scalp, neck, hands, feet, genitalia; lesion diameter 3.1 to 4.0 cm
17276	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), scalp, neck, hands, feet, genitalia; lesion diameter over 4.0 cm
17280	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), face, ears, eyelids, nose, lips, mucous membrane; lesion diameter 0.5 cm or less
17281	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), face, ears, eyelids, nose, lips, mucous membrane; lesion diameter 0.6 to 1.0 cm
17282	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), face, ears, eyelids, nose, lips, mucous membrane; lesion diameter 1.1 to 2.0 cm
17283	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), face, ears, eyelids, nose, lips, mucous membrane; lesion diameter 2.1 to 3.0 cm
17284	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), face, ears, eyelids, nose, lips, mucous membrane; lesion diameter 3.1 to 4.0 cm
17286	Destruction, malignant lesion (e.g., laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), face, ears, eyelids, nose, lips, mucous membrane; lesion diameter over 4.0 cm
17304	Chemosurgery (Mohs micrographic technique), including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and complete histopathologic preparation including the first routine stain (e.g., hematoxylin and eosin, toluidine blue); first stage, fresh tissue technique, up to 5 specimens
17305	Chemosurgery (Mohs micrographic technique), including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and complete histopathologic preparation including the first routine stain (e.g., hematoxylin and eosin, toluidine blue); second stage, fixed or fresh tissue, up to 5 specimens
17306	Chemosurgery (Mohs micrographic technique), including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and complete histopathologic preparation including the first routine stain (e.g., hematoxylin and eosin, toluidine blue); third stage, fixed or fresh tissue, up to 5 specimens

Code	Description
17307	Chemosurgery (Mohs micrographic technique), including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and complete histopathologic preparation including the first routine stain (e.g., hematoxylin and eosin, toluidine blue); additional stage(s), up to 5 specimens, each stage
17310	Chemosurgery (Mohs micrographic technique), including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and complete histopathologic preparation including the first routine stain (e.g., hematoxylin and eosin, toluidine blue); each additional specimen, after the first 5 specimens, fixed or fresh tissue, any stage (List separately in addition to code for primary procedure)
17311	Mohs micrographic technique, including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and histopathologic preparation including routine stain(s) (e.g., hematoxylin and eosin, toluidine blue), head, neck, hands, feet, genitalia, or any location with surgery directly involving muscle, cartilage, bone, tendon, major nerves, or vessels; first stage, up to 5 tissue blocks
17312	Mohs micrographic technique, including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and histopathologic preparation including routine stain(s) (e.g., hematoxylin and eosin, toluidine blue), head, neck, hands, feet, genitalia, or any location with surgery directly involving muscle, cartilage, bone, tendon, major nerves, or vessels; each additional stage after the first stage, up to 5 tissue blocks (List separately in addition to code for primary procedure)
17313	Mohs micrographic technique, including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and histopathologic preparation including routine stain(s) (e.g., hematoxylin and eosin, toluidine blue), of the trunk, arms, or legs; first stage, up to 5 tissue blocks
17314	Mohs micrographic technique, including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and histopathologic preparation including routine stain(s) (e.g., hematoxylin and eosin, toluidine blue), of the trunk, arms, or legs; each additional stage after the first stage, up to 5 tissue blocks (List separately in addition to code for primary procedure)
17315	Mohs micrographic technique, including removal of all gross tumour, surgical excision of tissue specimens, mapping, colour coding of specimens, microscopic examination of specimens by the surgeon, and histopathologic preparation including routine stain(s) (e.g., hematoxylin and eosin, toluidine blue), each additional block after the first 5 tissue blocks, any stage (List separately in addition to code for primary procedure)

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Canada's Drug and Health Technology Agency

CoLab Network

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About CADTH: CADTH is a not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.

About CoLab: CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with CADTH's Post-Market Drug Evaluation Program to produce credible and timely evidence on post-market drug safety and effectiveness.