NON-INTERVENTIONAL STUDY OF ADVANCED RENAL CELL CARCINOMA TREATMENT PATTERNS AND UNMET NEEDS

Title	Study of advanced renal cell carcinoma treatment patterns and unmet needs using real world claims and electronic medical record data.
Protocol number	A6181232
Protocol version identifier	01
Date of last version of protocol	4 October 2019
Research question and objectives	The study aims to assess treatment patterns and outcomes in advanced RCC patients in real world clinical practices across various real world databases. Four databases will be evaluated: IBM's Truven MarketScan Commercial, Optum Clinformatics, the IMS PharMetrics claims databases and The PanTher (which has both Humedica EMR data including EMR notes linked to Optum claims). The primary study objectives include: 1. **Treatment patterns:** Characterize first-line and subsequents lines of therapy. Treatment patterns will be summarized for the following therapy regimens: • immuno-oncology (IO) monotherapy; • IO+IO combo-therapy; • IO+tyrosine kinase inhibitor (TKI) combo-therapy; • TKI monotherapy; • Other. 2. **Analyze Cohorts of Interest:** To describe patient demographics and clinical characteristics, and select outcomes of interest among the following first-line advanced RCC cohorts of interest: • immuno-oncology (IO) monotherapy; • IO+IO combo-therapy; • IO+tyrosine kinase inhibitor (TKI) combo-therapy; • TKI monotherapy; • Other.

	3. Analyze Select Outcomes of Interest: • **Time to Treatment Failure (TTF)** - the time from therapy start to treatment discontinuation or therapy change (next line of therapy – switch or augment), end of enrollment, or death; • **Treatment Interruption** – those with gaps in treatment greater than allowable gap but who restart the same medication with no indication of switching or augmentation; • **Health Care Costs** (inpatient, outpatient, pharmacy, other); • **Health Care Utilization** (inpatient hospitalizations, ER, outpatient visits); • **Survival Time and Landmark Survival.** Mean/median survival time and % of population surviving 3, 6, and 12 months will be explored, although regimens are too new for extensive follow-up time. (Note: survival analysis will only be available in the Optum Clinformatics Database).
	PPD , PharmD, MSc Director, PPD New York, NY 10017 Email: PPD PPD Sr. Director, PPD Rockland, MA 02370 Email: PPD PPD , MD Title Address Email: PPD PPD Executive Director, PPD New York, NY 10017 Email: PPD

	PPD , MPH Director, PPD New York, NY 10017 Email: PPD PPD , MPH Manager, PPD New York, NY 10017 Email: PPD PPD Intern, PPD PPD New York, NY 10017 Email: PPD

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1. LIST OF ABBREVIATIONS

Table 1. Abbreviations

Abbreviation	Definition
AE	adverse event
AGI	Analysis Group, Inc.
aRCC	Advanced Renal Cell Carcinoma
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence interval
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiology Practices
Hb	hemoglobin
HR	hazard ratio
IRB	Institutional Review Board
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IO	Immuno-oncology
ISPE	International Society for Pharmacoepidemiology

Abbreviation	Definition
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LDH	lactate dehydrogenase
LLN	Lower limit of normal
LSLV	last subject last visit
mRCC	Metastatic Renal Cell Carcinoma
NCCN	National Comprehensive Cancer Network
OS	overall survival
PPPM	Per Patient Per Month
PFS	progression free survival
RCC	Renal cell carcinoma
SAP	Statistical Analysis Plan
SD	standard deviation
TKI	Tyrosine kinase inhibitor
TTD	time to treatment discontinuation

2. RESPONSIBLE PARTIES

Table 2. Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD	Sr Director, PPD	EMD Serono,	PPD MA, 02370
PPD PharmD	Co-investigator; Director, PPD PPD	Pfizer Oncology	PPD NY 10017
PPD , MD	PPD	University of IA	PPD IA
PPD	Director PPD	EMD Serono	PPD MA, 02370
PPD , PhD	Executive Director, PPD	Pfizer Global Product Development	PPD , NY 10017
PPD , MPH	Co-investigator; Director, PPD	Pfizer Real World Analytics	PPD , NY 10017

3. AMENDMENTS AND UPDATES

Table 3. Amendments and Updates

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason

4. RATIONALE AND BACKGROUND

Approximately 2% of all incident malignant tumors worldwide are caused by renal cancers.[1] In 2019, The American Cancer Society for Kidney Cancer in the United States estimates that there will be about 73,820 cases of kidney cancer. It also estimates that about 14,770 people will die from this disease.[2] RCC often gets diagnosed in advanced stages: ~25-30% of the patients are diagnosed at the metastatic disease stage.[3] Hence, patients with advanced disease often have high rates of morbidity and mortality.[4] Until 2005, cytokine therapy was the only approved post-surgical treatment of advanced RCC. These therapies were highly toxic and offered limited long-term clinical benefit in a majority of patients. This was followed by targeted therapies for treatment of mRCC with sorafenib in December 2005 and sunitinib in January 2006.[5] The US Food and Drug Administration (FDA)-approved tyrosine kinase inhibitors (TKIs) have expanded to included axitinib (January 2012) and pazopanib (October 2009).[6] The 5-year relative survival rates for these therapies have ranged from 10.4% for patients with later-stage disease involving distant metastases to 90.4% for early-stage localized disease.[7]

Treatment guidelines are determined by prognostic risk group using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria[8] or Memorial Sloan Kettering Cancer Center Prognostic Model (MSKCC).[9] According to 2019 NCCN guidelines, targeted therapy utilizing tyrosine kinase inhibitors, TKIs and/or VEGF antibodies (including pazopanib, sunitinib, bevacizumab, , axitinib, and cabozantinib) are recommended as first-and second-line treatments. Mammalian target of rapamycin (mTOR) (temsirolimus and everolimus) are also used in this setting. Immune checkpoint inhibitors, which alter the interaction between immune cells and antigen-presenting cells, are the new revolution in treatment options.[10]

In April 2018, the FDA approved the combination of the immuno-oncology (IO) checkpoint inhibitors ipilimumab and nivolumab for advanced RCC.[11] This combination is currently recommended as the new standard of care for first-line for treatment of metastatic RCC (mRCC) patients with intermediate or poor prognosis.[12]

This study will clarify current treatment patterns and unmet needs (eg, regimen adherence and discontinuation patterns) among the various regimens used to treat mRCC. This study characterize mRCC treated populations represented by the most prevalent treatment regimens and will quantify mRCC outcomes including treatment failure/duration of therapy, cost and utilization and survival in real world clinical practices toward demonstrating current unmet needs in mRCC.

5. RESEARCH QUESTION AND OBJECTIVES

The study aims to address the following key objectives among patient cohorts diagnosed with advanced/metastatic RCC:

Objective 1: Treatment patterns: Characterize first-line and subsequents lines of therapy. Treatment patterns will be summarized for the following therapy regimens:

- immuno-oncology (IO) monotherapy;
- IO+IO combo-therapy;
- IO+tyrosine kinase inhibitor (TKI) combo-therapy;
- TKI monotherapy;
- Other.

Objective 2: Analyze Cohorts of Interest: To describe patient demographics and clinical characteristics, and select outcomes of interest among the following first-line advanced RCC cohorts of interest:

- immuno-oncology (IO) monotherapy;
- IO+IO combo-therapy;
- IO+tyrosine kinase inhibitor (TKI) combo-therapy;
- TKI monotherapy;
- Other.

Objective 3: Analyze Select Outcomes of Interest:

- **Time to Treatment Failure (TTF)** - the time from therapy start to treatment discontinuation or therapy change (next line of therapy – switch or augment), end of enrollment, or death.

- **Treatment Interruption** – those with gaps in treatment greater than allowable gap but who restart the same medication with no indication of switching or augmentation.

- **Health Care Costs** (inpatient, outpatient, pharmacy, other).

- **Health Care Utilization** (inpatient hospitalizations, ER, outpatient visits).

- **Survival Time and Landmark Survival.** Mean/median survival time and % of population surviving 3, 6, and 12 months will be explored, although regimens are too new for extensive follow-up time. (Note: survival analysis will only be available in the Optum Clinformatics Database).

6. RESEARCH METHODS

This master protocol specifies more than one retrospective, longitudinal cohort studies that will be performed and replicated in various de-identified, real world administrative medical and pharmacy claims data and electronic medical records structured data. Leveraging multiple databases will optimize the study sample size and provide more robust foundation to addressing the research questions. The analyses will be performed using real world claims and EMR data, including Optum Clinformatics Claims, Truven Marketscan Commercial Claims, Pharmetrics Claims and the Optum PanTher containing the overlap of Optum claims and Humedica EMR structured data. It should be noted that contractual obligations associated with these datasources require that they not be merged or combined.

6.1. Study Design

Patients receiving aRCC treatement (see Table 4), between April 2018 and the present, who have no prior aRCC treatment in their claims history will be identified for this study. The index date for each analysis will be defined as the date of initiation of the aRCC treatment. Patients must have at least 2 RCC diagnoses at least 30 days apart to be included. Patients must also have 2 secondary malignancy ICD9 or ICD10 codes (often used in claims data to suggest cancer metastases) at least 30 days apart in the 12 months pre and one month post index aRCC treatment. CCI [redacted] Various algorithms and temporal relationships between the secondary malignancy codes, RCC diagnosis codes and other cancer codes were explored toward developing the criteria for metastatic advanced RCC for this study.

Study will require a minimum of 12 months of enrollment prior to the index date. Feasibility was assessed for various lengths of continuous enrollment criteria (3, 6 and 12 months post index date) toward understanding sample sizes available for analysis and follow-up periods. Study outcomes will be assessed for three patient cohorts (3, 6 and 12 month cohorts) according to their available months of continuous enrollment.

First line therapy cohorts will first be presented for all patients regardless of follow-up time available. Baseline characteristics, costs and utilization will be measured over the 6 months prior to the index date. Duration of therapy and utilization analysis will require at least 6 months of post-index enrollment, with sub-analysis preformed on the cohorts with 3-months and 12-months of post-index enrollment. Utilization and cost will be performed per-utilizer-per-month (PUPM), and then separately for each of the cohorts with 3-month, 6-month and 12-months of post-index enrollment.

The analysis will focus on, but is not limited to, the following regimens:

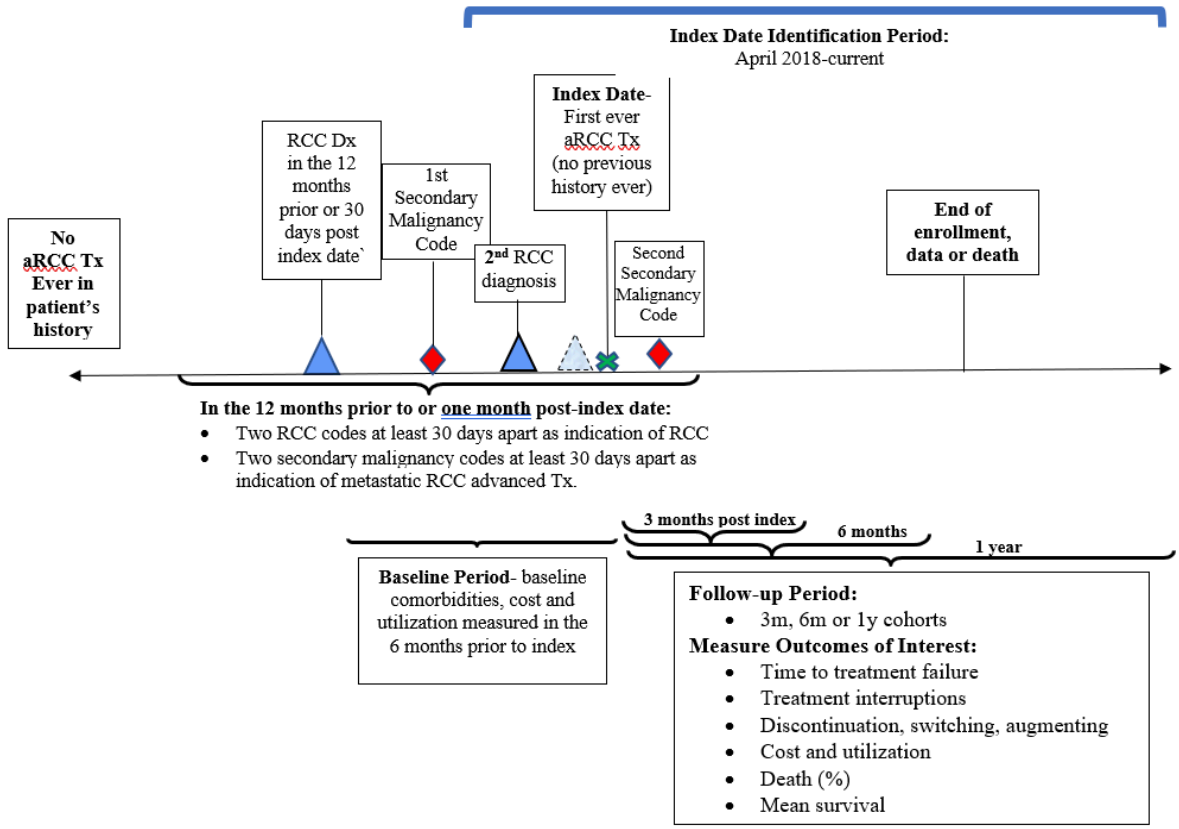
a. **Combo IO:** nivolumab combined with ipilimumab;

b. **Monotherapy TKI:** sunitinib, cabozantinib, and pazopanib;

c. **Combo TKI + IO:** avelumab in combination with axitinib, pembrolizumab in combination with axitinib;

d. **Other:** all others regimens.

Figure 1: Cohort Identification



Analysis 1. Treatment Patterns and Duration

The purpose of this initial analysis is to characterize the treatment patterns and treatment duration of adult patients with advanced and metastatic RCC across various real world claims databases (Truven, Optum and Pharmetrics claims). Treatment patterns for these various US population based claims dataset will be assessed for consistency and regimen-specific population differences, as well as assessing feasibility for sub-analyses.

In order to isolate lines of therapy of interest, all medications used for advanced RCC must be considered. Thus, lines of therapy will be performed considering the following RCC medications (see Table 4):

Table 4. Medications of Interest

Drug Class	Ingredient	Brand Name	Dosage Form	Mechanism
TKI	Pazopanib	Votrient	Oral	Tyrosine Kinases Inhibitor
TKI	Sunitinib	Sutent	Oral	Multiple receptor tyrosine kinases (RTKs)
TKI	Axitinib	Inlyta	Oral	Kinase inhibitor
TKI	Caboznatinib	Cabometyx/Cometriq	Oral	New Novel TKI
TKI	Sorafenib	Nexavar	Oral	Multikinase inhibitor
TKI	Levantinib	Lenvima	Oral	RTK inhibitor
TKI	Erlotinib	Tarceva	Oral	Epidermal Growth Factor Receptor tyrosine kinase inhibitor
mTOR	Temsirolimus	Torisel	Both oral and IV	Inhibitor of mammalian target of rapamycin
mTOR	Everolimus	Afinitor	Both oral and IV	Mammalian target if rapamycin inhibitor
IO	Ipilimumab	Yervoy	Injection	Human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody
IO	Nivolumab	Opdivo	Injection	Checkpoint monoclonal Antibody PD-1 Inhibitor
IO	Atezolizumab	Tecentriq	Injection	Checkpoint monoclonal Antibody PD-L1 Inhibitor
IO	Durvalumab	Imfinzi	Injection	Checkpoint monoclonal Antibody PD-L1 Inhibitor
IO	Pembrolizumab	Keytruda	Injection	Checkpoint monoclonal Antibody PD-1 Inhibitor
IO	Avelumab	Bavencio	Injection	Checkpoint monoclonal Antibody PD-L1 Inhibitor
IO	Bevacizumab	Avastin	Injection	Recombinant monoclonal antibody VEGF/VEGFR Inhibitor

First-line and subsequent lines (up to 3) of monotherapy and combo-therapy regimens for aRCC patients will be identified and the following metrics will be considered for first-line of therapy:

- Time from first ever metastatic diagnosis to first line regimen;
- Duration of first line therapy;
- Patterns of switching, augmentation and discontinuation;
- Treatment interruptions.

Treated Period Follow-Up. Patients will be followed over the period treated with advanced RCC therapy. Time treated will be defined as the time from the index date to the date of the end of the last advanced metastatic RCC prescription (end of supply for orals/administration date plus 30 days for injectibles), end of enrollment, end of follow up, or death (see more specifics on oral versus injectable rules in 6.3.1 Variables section of this protocol).

Analysis 2. Describe various treated populations of interest by demographics, clinical characteristics, as well as cost and utilization

Describe the demographics and other baseline characteristics of the first-line treated cohorts of interest identified in the treatment patterns analysis (Analysis 1) for RCC patient as follows:

Baseline Characteristics (see 6.3.2 Baseline Characteristics):

- Age at index;
- Gender;
- Race;
- Region;

- Payor;
- Clinical characteristics: Quan-Charlson Comorbidity Index (CCI) scores and baseline comorbidities;
- Prior treatment (6 months prior) - nephrectomy, radiation/ablation, interferon, high-dose interleukin-2, other anti-neoplastic medications;
- Secondary malignancy locations (6 months prior);
- Baseline costs of care (6 months prior);
- Baseline health care resource utilization (6 months prior).

Analysis 3: Evaluate the key outcomes of interest for advanced RCC therapy regimens toward demonstrating existing unmet needs in RCC given currently available therapies (eg, ipilimumab/nivolumab).

Treatment duration, discontinuation, interruption, switching and therapy augmentation will be presented, as will the burden of disease costs and health care utilization. Survival will also be explored, although regimens are too new for extensive follow-up time.

Overall Outcomes Study Period. For the outcomes analysis, follow-up will be defined as the time from the index date to the end of specified follow up period of 6 months, end of enrollment, or death. Follow-up may vary given sample sizes of study population, with by subanalysis using 1-year or 2-years of follow-up time from study index date for certain sub-populations.

Outcomes include:

- **Time to Treatment Failure (TTF)** – First line time to treatment failure (TTF) is defined as the time from first-line therapy start to treatment discontinuation for any reason, including switched, augmented therapy, end of enrollment, death.
- **% continuing –** those with no gap in therapy greater than 30 days and who do not begin a new treatment during the study period.
- **% discontinuing –** those with gap in therapy greater than 30 days and who do not begin a new treatment.
- **% with treatment interruption -** those with gap in therapy greater than 30 days but who eventually continue the original treatment (have an additional administration or refill) and do not switch or augment therapy during the study period.
- **% switching –** those with gap in therapy greater than 30 days and who begin a new treatment.
- **% augmenting –** those who begin a new treatment but continue using the original treatment (have an additional administration or refill) and do not have a gap in therapy greater than 30 days of their original treatment.
- **Overall and aRCC Follow-Up Costs:** Total and RCC-specific pharmacy, medical costs from aRCC therapy index through follow-up period (costs summarized as: mean, median costs per patient and costs per patient per month).

- **Overall and aRCC Follow-Up Utilization:** Total and RCC-specific inpatient, ER, outpatient visits from aRCC therapy index through follow-up period (utilization will be summarized as: mean, median utilization per patient and utilization per patient per month).
- **Overall landmark survival:** Using Optum claims and PanTher data, landmark survival will be described and compared over follow-up time periods (3, 6, 12 months).
- **Mean/Median Survival:** Using Optum claims and PanTher data median survival time will be described and compared over follow-up time periods determined after feasibilitied assessments of cohorts of interest.

6.2. Setting

Anonymized patient data available in US admistrative research database will be used for this study. This study will utilize various databases including the Truven Marketscan Commercial, Optum Clinformatics DOD (includes death data from the Social Security Death Masterfile), and Pharmetrics Claims data all representing patients enrolled in US commercial health plans, Medicare or Medicaid. Plan enrollment information is available with these data. The Optum PanTher database will also be used as it represents patients with both Optum claims data and Humedica EMR data, which includes a large database of terms extracted from EMR notes fields. Sub-analysis specified will use wider structured data elements, such as reasons for treatment failure, which may be extracted from the EMR notes fields.

Inclusion and exclusion criteria are detailed below in Sections 6.2.1 and 6.2.2. All patients meeting eligibility requirements will be included in the analyses. The resulting population is expected to be representative of patients with the types of insurance coverage available in the source databases. The databases listed in Section 6.4 will be evaluated. This protocol may also be amended to include additional databases over time.

6.2.1. Inclusion Criteria

Subjects will be selected irrespective of their survival status. Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- **Index date:** The first prescription or administration of one of the medications indicated for advanced RCC recorded in the database between April 2018-March 31, 2019, among those with no aRCC treatment in their history.

- Age 18 years or older in the year of the index first line therapy prescription.

- 2 or more RCC diagnoses (ICD-9: 189.0; ICD-10: C64.1, C64.2, C64.9) at least 30 days apart, in the 1 year prior to the index date until 30 days post index date.

- 2 or more code for secondary malignancy codes indicating possible diagnoses for metastatic disease at least 30 days apart, in the 1 year prior to the index date until 30 days post index date. (ICD-9: xx-199.xx; ICD-10: C77-C79, except ICD9: 198.0 Secondary malignant neoplasm of the kidney and ICD10: C79.0 Secondary malignant neoplasm of the kidney and renal pelvis).
    - CCI [redacted]
- Continuous enrollment from 12 months prior to the index date. Patients will be required to have continuous enrollment from their index date until the end of the available data. This will allow for sub-analysis of cohorts with 3 months, 6 months and 12 months of available data.

6.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

- Received advanced treatment prior to the study index date.
- Prescription records with negative days of supply will be excluded from all the analyses except in cost variable calculation. The day of supply for claims with missing or 0 days will be imputed.
- Only one RCC diagnosis in the 12 months prior or one mont post index date.
- Patients with data for analysis (<3 months post index date).

6.3. Variables

6.3.1. Treatment Pattern Variables

Table 5. Treatment Pattern Variables

Variable	Operational definition
Initial (1L)Treatment Regimen	The first treatment regimen prescribed following a primary and secondary diagnosis of advanced/metastatic disease.
Monotherapy vs Combo therapy	Categorical: Yes/No Combo therapy is defined by a second medication filled on or within 30 days of the original medication and the originical medication is filled subsequently. CCI [redacted]
Time to FL treatment received	Continuous: days Length of time (days) from the first mRCC diagnosis (first ever secondary malignancy code associated with RCC) to first line therapy prescription.
Treatment discontinuation date (by LoT) – to be used for time to treatment failure (TTF) and time to next line of therapy	Date Treatment discontinuation indicating the end of LOT will be identified as the earliest of: • For oral therapy: to the run-out date of the last prescription (ie, date of last prescription plus days supply) in the same treatment line. • For non-oral therapy: 30 days after the last observed prescription/administration prior to at least a 30 day gap in therapy of all agents included in the first line of therapy. • 1 day before a new prescription/administration date, whichever occurred earlier. • For multiple drug regimens: the above would be triggered by the last prescription/administration in the regimen. • Death. • End of enrollment.
Days of continuous treatment (by LoT)	Continuous: days The duration of each LOT will be measured from the first prescription or administration of line of therapy medication(s) to the end of the line of therapy, allowing for 30 day allowable gaps in therapy.
Treatment Continuation	Categorical (Y/N) There is no >30 day gap (ie, persistent treatment) for the index medication during follow-up period.

Variable	Operational definition
Treatment Interruption	Categorical (Y/N) At least one instance of >30 day gap (ie, non-persistent treatment) for the index medication during follow-up period or LOT followed by resuming therapy (not mutually exclusive with switch, augment, discontinuation, but a sub-group within LOT).
Interrupted treatment duration	Continuous: days Time from index medication to treatment discontinuation for those within treatment interruptions (>30 day gaps). Represents the time between index and end of last treatment, including any treatment gaps.
Regimen change (switching)	Categorical: Yes/No At least one non-index advanced/metastatic RCC medication during or after the period of the last persistent index medication prescription's days supply plus the 30 day gap (and before re-initiation of index medication or follow-up, if after).
Regimen change (augmentation)	Categorical: Yes/No Addition of treatment to initial therapy prescribed, ie, initiation of a new therapy different from the initial therapy while continuation of the initial therapy.
Line of therapy definitions	Categorical: 1L vs. 2L vs. >=3L.
Treatment sequence	Categorical: Based on observed treatment sequences. Treatment Sequence – Sequence of successive therapies for mRCC from 1L to 2L to 3L (stop after 3L).
Patient's status at end of follow-up	Categorical: end of enrollment, end of data availability, death. Patient is in one of the following mutually exclusive categories at the end of follow-up.

6.3.2. Baseline Variables

Table 6. Baseline Variables

Variable	Operational definition
Baseline demographics	
Index Date	Date of first RCC diagnosis on record
Index Year	Index year for the patient
Age	Continuous: Years Patient age at index date
Sex	Categorical: Male or female
Insurance Coverage	Categorical: Commercial, Medicare, or Medicaid
US Region	Categorical: Northeast, Midwest, South, West
Race	Categorical: based on each database
Clinical characteristics	
Time to systemic therapy <1 year	From IMDC: <1 year from time of diagnosis to systemic therapy
NCI Charlson comorbidity index (DCI)	Categorical: 0, 1-2, 3+
History of smoking	Categorical: Yes/No Prior history of smoking – record of smoking cessation medication or V code.
History of systemic therapy	Categorical: Yes/No A record of being given certain systemic drugs (interferon, interleukin 2, gemcitabine and doxorubicin)
History of surgical resection	Categorical: Yes/No History of nephron sparing or radical nephrectomy. ICD-10-CM Z90.5/ICD-9-CM V45.73 Acquired absence of kidney.

Variable	Operational definition
History of radiation therapy	Categorical: Yes/No **ICD-10-CM** Z51.0/ICD-9-CM V58.0 Encounter for radiotherapy. **ICD-10-PCS** › D › Urinary System: • DT0 Beam Radiation; • DT1 Brachytherapy; • DT2 Stereotactic Radiosurgery; • DTY Other Radiation. **CPT Codes:** 77401 Radiation treatment delivery, superficial and/or ortho voltage, per day; 77402 Radiation treatment delivery, >1MeV; simple; 77407 intermediate; 77412 complex. <u>New Codes</u> 77085 Dual-energy x-ray absorptiometry (DXA), bone density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine), including vertebral fracture assessment. 77086 Vertebral fracture assessment via dual energy X-ray absorptiometry (DXA). 77306 Teletherapy isodose plan; simple (1 or 2 unmodified ports directed to a single area of interest), includes basic dosimetry calculation(s).

Variable	Operational definition
	77307 complex (multiple treatment areas, tangential ports, the use of wedges, blocking, rotational beam, or special beam considerations), includes basic dosimetry calculation(s). 77316 Brachytherapy isodose plan; simple (calculation[s] made from 1 to 4 sources, or remote afterloading brachytherapy, 1 channel), includes basic dosimetry calculation(s). 77317 intermediate (calculation[s] made from 5 to 10 sources, or remote afterloading brachytherapy, 2-12 channels), includes basic dosimetry calculation(s). 77318 Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple. 77385 Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple. 77386 complex. 77387 Guidance for localization of target volume for delivery of radiation treatment delivery, includes intrafraction tracking, when performed. <u>Deleted Codes (may be in the historic data, though no longer in use)</u> 72291 Radiological supervision and interpretation, percutaneous vertebroplasty, vertebral augmentation, or sacral augmentation (sacroplasty), including cavity creation, per vertebral body or sacrum; under fluoroscopic guidance. 72292 under CT guidance. 74291 Cholecystography, oral contrast; additional or repeat examination or multiple day examination. 76645 Ultrasound, breast(s) (unilateral or bilateral), real time with image documentation. 76950 Ultrasonic guidance for placement of radiation therapy fields. 77080 Dual-energy X-ray absorptiometry (DXA), bone density study, 1 or more sites; axial skeleton (eg, hips, pelvis, spine). 77305 Teletherapy, isodose plan (whether hand or computer calculated); simple (1 or 2 parallel opposed unmodified ports directed to a single area of interest). 77310 intermediate (3 or more treatment ports directed to a single area of interest).

Variable	Operational definition
	77315 complex (mantle or inverted Y, tangential ports, the use of wedges, compensators, complex blocking, rotational beam, or special beam considerations). 77326 Brachytherapy isodose plan; simple (calculation made from single plane, 1 to 4 sources/ribbon application, remote afterloading brachytherapy, 1 to 8 sources). 77327 intermediate (multiplane dosage calculations, application involving 5 to 10 sources/ribbons, remote afterloading brachytherapy, 9 to 12 sources). 77328 complex (multiplane isodose plan, volume implant calculations, over 10 sources/ribbons used, special spatial reconstruction, remote afterloading brachytherapy, over 12 sources). 77403 Radiation treatment delivery, single treatment area, single port or parallel opposed ports, simple blocks or no blocks; 6-10 MeV. 77404 11-19 MeV. 77406 20 MeV or greater. 77408 Radiation treatment delivery, 2 separate treatment areas, 3 or more ports on a single treatment area, use of multiple blocks; 6-10 MeV. 77409 11-19 MeV. 77411 20 MeV or greater. 77413 Radiation treatment delivery, 3 or more separate treatment areas, custom blocking, tangential ports, wedges, rotational beam, compensators, electron beam; 6-10 MeV. 77414 11-19 MeV. 77416 20 MeV or greater. 77418 Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session. 77421 Stereoscopic X-ray guidance for localization of target volume for the delivery of radiation therapy.

Variable	Operational definition
Location of metastasis	Categorical: by location (% of patients for each): □ Lymph nodes (ICD9-196.xx, ICD10 – C77) □ Lung (ICD9-197.0x, ICD10-C78.00) □ Liver (ICD9-197.7x, ICD10-C78.7) □ Brain (ICD9-198.3x, ICD10-C79.31) □ Bones (ICD9-198.5x, ICD10-79.5x) □ Adrenal gland (ICD9-198.7x, ICD10-79.7) □ Other (ICD9 196.xx-199.xx and ICD10 C77-C80 exclusive of above categories)
Severe renal impairment	Categorical: Yes/No ICD-9: 588.89, 588.9, 593.9, 274.02, 274.03 ICD-10: M10.3x, M1A.3x, N25.89, N25.9
Moderate-to-severe hepatic impairment	Categorical: Yes/No ICD-9: 571, 572, 573 ICD-10: K70.4x, K71.0, K71.1X, K72, K73, K75, K76, K77
Constipation	Categorical: Yes/No • ICD9 code: 564.0x; ICD10 code: K59.0
Nausea	Categorical: Yes/No ICD9 code: 787.01; ICD10 code: R11.0, R11.2

6.3.3. Outcomes Variables

Table 7. Outcomes Variables

Variable	Operational definition
Days to Treatment Failure (TTF)	Time to treatment failure (TTF) is defined as the time from therapy start to treatment discontinuation for any reason, including switched, augmented therapy, end of enrollment, death.
Discontinuation	% discontinuing – those with gap in therapy greater than 30 days and who do not begin a new treatment.
Switching	% switching – those with gap in therapy greater than 30 days and who begin a new treatment.
Augmentation	% augmenting – those who begin a new treatment but continue using the original treatment (have an additional administration or refill) and do not have a gap in therapy greater than 30 days of their original treatment.
% Survived 3,6, 12 months	Mean/Median Survival Time (Days): Survival time will be described over 3,6, 12 months given follow-up time available in the data. Overall survival is defined as the length of time from index date of RCC diagnosis to patient death (or index date associated with FL Tx?) or end of available data for with no death indication. Overall landmark survival: described and compared over follow-up time periods (3,6, 12 months). Percentage of patients alive at 3,6, 12 months.
Overall Survival Time	Continuous: days Overall survival is defined as the length of time from index date of RCC diagnosis to patient death (or index date associated with FL Tx?)

6.3.4. Cost and Utilization Variables

Table 8. Cost and Utilization Variables

Variable	Operational definition
All-cause Health Resource Utilization: Total inpatient, ER, outpatient visits from index aRC period.	Any healthcare resource use per patient per month (PPPM) will be examined for each regimen-based cohort under each LOT and will further be categorized as the following: Occurrence of (Categorical: Yes/No): • any inpatient stay; • any outpatient visit; • any ER visit. Number of visits (Continuous): • inpatient stays; • outpatient visits; • ER visits. Inpatient LOS (Continuous: days).

Variable	Operational definition
aRCC HR Utilization: RCC-specific inpatient, ER, outpatient visits from aRCC therapy index through follow-up period.	RCC-related healthcare resource use per patient per month (PPPM) will be examined for each regimen-based under each LOT. Medical claims will be considered RCC-related if they have an ICD-9/10-CM diagnosis code for RCC in any position on the claim. Occurrence of (Categorical: Yes/No): • any inpatient stay; • any outpatient visit; • any ER visit. Number of visits (Continuous): • inpatient stays; • outpatient visits; • ER visits. Inpatient LOS (Continuous: days).

Variable	Operational definition
All-cause Healthcare Costs **Overall** medical costs and pharmacy costs from aRCC therapy index through follow-up.	Continuous: dollars All-cause healthcare costs will be examined for each for each regimen-based cohort under each LOT. Costs w adjusted to 2019 US dollars (USD) using the medical care component of the Consumer Price Index (CPI). He costs PPPM will be provided, and will be further categorized as: • Inpatient stay costs; • Outpatient costs; • ER visit costs; • Pharmacy costs (medical); • Pharmacy costs (pharmacy); • Total costs.
mRCC-related Healthcare Costs RCC-specific pharmacy, medical costs from aRCC therapy index through follow-up period	Continuous: dollars aRCC therapy Pharmacy claims for medication used to treat RCC will be included in the pharmacy costs usin pharmacy claim data. RCC-related healthcare costs will be examined for each regimen-based cohort under each LOT. Costs will be adjusted to 2019 US dollars (USD) using the medical care component of the Consumer Price Inc Health care costs PPPM will be provided, and will be further categorized as: • Inpatient stay costs; • Outpatient costs; • ER visit costs; • Pharmacy costs (medical claims); • Pharmacy costs (pharmacy claims); • Total costs (total pharmacy + total medical.

6.4. Data Sources

Results will be replicated to the extent possible across various real world databases in order to confirming and validate results across data sources. At the start of the study, four databases will be evaluated. IBM's Truven MarketScan Commercial, Optum Clinformatics, the IMS PharMetrics claims databases and The PanTher (which has both Humedica EMR data including EMR notes linked to Optum claims). After population sizes are assessed in the various databases, sub-analysis for populations with adequate patient data will be clarified in an amendment to this protocol.

Optum Clinformatics:

Optum Clinformatics has access to a proprietary research database containing claims and enrollment data dating back to 1993 with the opportunity to link patient and physician survey data to pharmacy and medical claims, medical record data, socioeconomic measures, and clinical laboratory results on over 123 million lives. Underlying information is geographically diverse across the United States, and is updated frequently. The research activities utilize de-identified data from the research database except in limited instances where applicable law allows the use of patient identifiable data.

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The claims history is a profile of all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications. Pharmacy claims are typically added to the research database within 6 weeks of dispensing.

Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for virtually all types of provided services, including specialty, preventive and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers, eg, physicians, use the HCFA-1500 format. Claims for facility services submitted by institutions, eg, hospitals, use the UB-82 or UB-92 format. Medical claims include: multiple diagnosis codes recorded with the ICD-9-CM diagnosis codes; procedures recorded with ICD-9-CM procedure codes, Current Procedural Terminology (CPT), or Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include any drugs administered in hospital. Approximately 6-9 months following the delivery of services is required for complete medical data, therefore patients will be followed for this additional time period. In summary, the analysis window will include data from 24 months pre index date, and 24 months post index date.

Integrated Optum E.H.R and Claims (PanTher)

Integrated Optum E.H.R. (formerly Humedica) clinical data and Optum Clinformatics administrative claims data (United enrollees) are included in the Optum PanTher Database. Estimated to be approximately 15% of the Optum Claims lives are represented in this database. This asset combines the clinical specificity of the Optum E.H.R. data with the administrative claims data which includes cost data, pharmacy fill data, and enrollment time periods among other things.

The Optum EHR database has broad geographic representation and includes patient demographic and clinical information, including diagnosis, medications, labs, procedures, microbiology and biomarkers. Optum EHR also extracts data from physician notes using industry-leading Natural Language Processing (NLP).

The Optum EHR database includes patient records from multiple EMR systems which capture data from different sites of care and a full spectrum of inpatient and outpatient treatment (eg, both Written Prescription and Inpatient-Administered medications). Records are completely de-identified and are fully compliant with the Health Insurance Portability and Accountability Act (HIPAA). Data is sourced from large Integrated Delivery Networks (IDN) with over 60% of patients having both outpatient and hospital information. The remainder of the patients are from large multi-specialty physician practices.

Outpatient laboratory test results are available for subpopulations of the research database. Standard Logical Observation Identifiers Names and Codes (LOINC) coding is used to define specific tests and results. Test results data can be linked to the other health care utilization and pharmacy claims data in the research database. Results included in the database are typically from blood-based tests (eg, low-density lipoprotein, glycated hemoglobin levels) that are sent for processing to two of the largest laboratory facilities in the country. Data are available for approximately 30-40% of members who were administered the test, depending on the test.

Truven Marketscan Commercial:

The MarketScan data warehouse is a family of databases from commercially insured lives. Pfizer licenses the following data sources: healthcare claims, hospital drug/discharge information with links to claims data and Medicare Supplemental files. The Truven Health MarketScan Research Databases reflects the combined healthcare service use of individuals covered by Truven Health clients (including employers, health plans, and hospitals) nationwide. Truven Health builds databases comprise the healthcare experience of the clients' covered populations, as well as information about the populations themselves and the providers that serve them. MarketScan Research Databases provide detailed cost, utilization, and outcomes data for healthcare services performed in both inpatient and outpatient settings. In the claims databases, the medical services are linked to outpatient prescription drug claims and person-level enrollment data using unique enrollee identifiers.

The MarketScan Commercial Database contains the healthcare experience of privately insured individuals. Coverage is provided under a variety of fee-for-service, fully capitated, and partially capitated health plans, including preferred provider organizations, point of service plans, indemnity plans, and health maintenance organizations.

The Enrollment Detail Table provides a single record per month of enrollment for each enrollee, with detailed demographic information.

Claims are not included in the database until they have been adjudicated; there is a lag of approximately six months after the close of a calendar year or a quarter between services provided and their inclusion in the Research Databases. However, the Early View Database has a 90-day lag that includes paid amounts for 100 percent of prescription drugs, approximately 85 percent of physician office visits, and approximately 70 percent of hospital claims. The MarketScan Early View Database includes all of the components found in the standard MarketScan Commercial and Medicare Supplemental Databases. It includes standardized inpatient, outpatient, pharmaceutical, and health-plan enrollment data. The MarketScan Early View Database captures healthcare services incurred up to 90 days before data release and includes only adjudicated claims. However, the medical component of care for some patients will not be complete, since some claims (particularly inpatient claims) take longer to be adjudicated. Because this study is examining only comorbidities prior to and treatments during or prior to glasdegib initiation fully adjudicated claims are not required and all available data will be used including Commercial, Medicare Supplemental, and Early View Databases.

Pharmetrics Plus

The PharMetrics Plus database is comprised of fully adjudicated medical and pharmacy claims. Specifically, it contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs and enrollment information. With PharMetrics Plus, you can track an enrolled patient across all sites of care: hospital, specialist, emergency room, pharmacy, primary care, ambulatory, and more.

There are over 140 million unique enrollees with both medical and pharmacy benefits. The enrollee population in the PharMetrics Plus database is generally representative of the under 65 commercially insured population in the US with respect to both age and gender. We have over 10 million enrollees who are over 65 years of age. Longitudinal enrollment range of individuals in the database on average is 36 months and more than 42 million patients have 3 or more years of continuous enrollment.

The PharMetrics Plus database offers a diverse representation of payer types, provider specialties, geographic granularity and linking capabilities. Patient region and state are standard patient variables and zip3 is optional and available for a subset of patients. Provider identification is an optional variable and available for a subset of providers using the National Provider Identifier. Patient linking is achieved by leveraging IQVIA's patented

technology for the subset of patients assigned a unique, encrypted patient key in multiple databases. Please note that there can be limits to the provisioning of the combination of some variables when linking is enabled.

Commercial insurance is the most frequent plan type captured for the enrollee population but other types are also found, including Commercial Medicare, Commercial Medicaid, Self-Insured, Indemnity and Others. In addition to standard fields such as inpatient and outpatient diagnoses and procedures, retail and mail order prescription records, PharMetrics Plus has detailed information on the pharmacy and medical benefit (copayment, deductible), the inpatient stay and provider details (provider specialty included in all extracts). Economic variables include the negotiated rate between the plan and providers (allowed) and the actual amount paid by health plans to the provider for all services rendered. Charge amount is also available for a subset of claims. Other data elements include dates of service, demographic variables (age, gender, and geographic region), product type (eg, HMO, PPO), payer type (eg, commercial), and start and stop dates of health plan enrollment. All data are HIPAA compliant to protect patient privacy.

While the most recent release of the PharMetrics Plus database is typically used to create all client deliverables, there may be a 4-6 month lag with newer claims largely owing to the typical processing time for claims adjudication mentioned above.

6.5. Study Size

The sample size for this study is fixed by the duration of the observation window. No formal sample size computation was performed as it is not applicable for this observational study. All patients who meet the entry criteria will be included in the analyses.

6.6. Data Management

All databases used in this study comply with both the spirit and the letter of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). These databases meet the criteria for a limited-use dataset and contain none of the data elements prohibited by HIPAA for limited-use datasets. Tables will be regenerated on a periodic basis based on scheduling of database updates and refreshes. This study will use a combination of analytical tools, Boston Health Economic's Instant Health Data (IHD) tool, with ad hoc programming performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC) or R software for statistical computing and graphics supported by the R Foundation for Statistical Computing.

6.6.1. Record Retention

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study.

6.7. Data Analysis

The planned statistical methods to be used in this study are descriptive and are specified in this section. No separate Statistical Analysis Plan is required.

Descriptive statistics will be used to report all study variables including demographic and clinical characteristics and treatment patterns. Categorical variables will be summarized using frequency counts and percentages. Continuous and cost variables will be summarized using means, medians, and standard deviations, minimum, maximum, 25th percentile, and 75th percentiles for the 3 cohorts with corresponding 3, 6 and 12 month follow-up periods. Summary cost metrics will be calculated using the entire population as the denominator, including those not reporting costs as having 0 costs. Standardized differences, defined as the absolute difference in sample means divided by an estimate of the pooled standard deviation of the variable, will be calculated for each variable. Additionally, costs and event rates per patient per month (PPPM) will be reported. Kaplan-Meier curves will be generated to examine time-to-event variables (duration of therapy and survival).

Duration of therapy calculations, which hinge on how frequently each of the medications considered are administered for injectibles, and days of supply represented by a prescription for orals will necessitate imputation of days of supply for medications with days supply values which do not represent the number of expected days between administrations or refills. The following imputations will be performed for the medications of interest to allow for treatment patterns and duration of therapy.

Table 9. Imputations of Days Supply

Ingredient	Route of Administration	Imputed Days Supply
Temsirolimus	Both oral and IV	7
Everolimus	Both oral and IV	28
Ipilimumab	Injection/Oral	21
Nivolumab	Injection/Oral	28
Atezolizumab	Injection	21
Durvalumab	Injection	28
Pembrolizumab	Injection	21
Avelumab	Injection/Oral	14
Bevacizumab	Injection/Oral	14

6.8. Quality Control

This is a retrospective study, so issues of quality control at study sites, eg, data queries, do not apply. Analyses are programmed according the specifications in the protocol, and if applicable, the statistical analysis plan and documented in a programming plan. Final deliverables are reviewed and verified by a second, independent data scientist using IHD. All quality checks will be documented.

6.9. Limitations of the Research Methods

When using claims and secondary databases as data sources for comparative analyses, several limitations may exist. Patients are not randomized to treatment, which may cause confounding. Multivariate analyses or matching techniques, such as propensity score matcing, can be used to address this confounding. It is difficult to assess disease severity, stage, and disease progression using claims data alone. As such, electronic medical records and specialty oncology data sources such as Concerto or Flatiron will be used when available to assess and supplement claims information on these factors. Additionally, claims may contain incomplete and inaccurate data on days supply and dosage of prescriptions, which may affect persistence and dosage change evaluations. Finally, there may be errors in claims coding, which may affect analyses and patient counts. No causal inference can be made in an observational study, and findings may not be generalizable to other populations.

6.10. Other Aspects

Not applicable.

7. PROTECTION OF HUMAN SUBJECTS

7.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

7.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

7.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This study does not require IRB approval.

7.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices for retrospective observational studies, described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and the GRACE (Good ReseArch for Comparative Effectiveness) Principles.

8. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves claims and EMR data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the *minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met*.

9. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For all publications relating to the Study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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11. LIST OF TABLES

12. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Comorbidities	ICD-9-CM Codes	ICD-10-CM Codes
Quan CCI comorbidities (Quan 2005)		
AIDS	042.x–044.x	B20.x–B22.x, B24.x
Any malignancy	140.x–172.x, 174.x–195.8,	
200.x–208.x, 238.6	C00.x–C26.x, C30.x–C34.x, C37.x–	
C41.x, C43.x, C45.x–C58.x, C60.x–		
C76.x, C81.x–C85.x, C88.x,		
C90.x–C97.x		
Cerebrovascular disease	362.34, 430.x–438.x	G45.x, G46.x, H34.0, I60.x–I69.x
Chronic pulmonary disease	416.8, 416.9, 490.x–505.x,	
506.4, 508.1, 508.8	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x,	
J68.4, J70.1, J70.3		
Congestive heart failure	398.91, 402.01, 402.11, 402.91,	
404.01, 404.03, 404.11,		
404.13, 404.91, 404.93,		
425.4–425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0,	
I42.5–I42.9, I43.x, I50.x, P29.0		
Dementia	290.x, 294.1, 331.2	F00.x–F03.x, F05.1, G30.x, G31.1
Diabetes with complications	250.4–250.7	E10.2–E10.5, E10.7, E11.2–E11.5,
E11.7, E12.2–E12.5, E12.7, E13.2–		
E13.5, E13.7, E14.2–E14.5, E14.7		
Diabetes without chronic complications	250.0–250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9,
E11.0, E11.1, E11.6, E11.8, E11.9,		
E12.0, E12.1, E12.6, E12.8, E12.9,		