MINI-SENTINEL SYSTEMATIC EVALUATION OF HEALTH OUTCOME OF INTEREST DEFINITIONS FOR STUDIES USING ADMINISTRATIVE DATA

LYMPHOMA REPORT

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May 12, 2011

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Systematic Evaluation Of Health Outcome Of Interest Definitions For Studies Using Administrative Data

Lymphoma Report

I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT

The U.S. Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. To perform this active surveillance, it is necessary to develop and understand the validity of algorithms for identifying health outcomes of interest in administrative data. Thus, the goal of this project was to identify algorithms used to detect selected health outcomes of interest using administrative data sources and describe the performance characteristics of these algorithms as reported by the studies in which they were used. This report summarizes the process and findings of the lymphoma algorithm review.

B. SUMMARY OF FINDINGS

Only one study was identified that validated four algorithms used in an administrative database to identify lymphoma. It is summarized in Table 3.[1] The authors considered the best algorithm to be one that identified cases using a number of requirements, either multiple diagnosis codes within 2 months or a diagnosis code plus other cancer-related procedures or drug dispensations. This algorithm had a PPV of 56.6%, sensitivity of 88.3%, and specificity of 99.3%. This study used registry-confirmed cases as the reference standard, and therefore may have misclassified some true positive cases as false positives.

It is notable that this validation study[1] included an analysis to determine the impact of the algorithm performance characteristics on rate ratio estimates in a hypothetical cohort study examining lymphoma as an outcome of drug exposure. Rate ratios were reduced by 0.151 to 0.223, depending on the estimated prevalence of the outcome. A higher prevalence of the outcome in the study population led to greater bias in the rate ratio estimate.

There were 10 other studies that used administrative databases, but they did not validate the algorithms. These are summarized in Table 4.[2-11] They generally all used either the International Classification of Disease (ICD) disease codes or the Current Procedural Terminology (CPT) codes. A multitude of other studies used cancer registries to identify cases. The algorithms described in these studies are not applicable to administrative data since they only include confirmed cases and use registry-specific coding systems.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

There are many different types of lymphoma. They can be separated into categories based on several different properties, most of which do not track well with the ICD coding methodology. In particular, they can be separated for etiologic purposes into T-cell and B-cell lymphomas, for outcome purposes into curable and non-curable lymphomas, or for tracking intensity of therapy purposes into aggressive or non-aggressive lymphomas. The historical approach of separating into Hodgkin or non-Hodgkin lymphoma is perhaps not as globally useful as it once was.

For purposes of pharmacoepidemiologic studies, which provided the impetus for this Mini-Sentinel report, it is logical to cast a wide net of lymphoproliferative diseases and include lymphoid leukemias and perhaps even plasma cell disorders as they are more biologically related to “lymphomas” than their

naming convention might suggest. The one validation study that was conducted excluded plasma cell diseases but found two basic algorithms with reasonable performance characteristics, though excellent higher PPV would be desirable.[1] The combination of these algorithms led to what the authors felt was the best algorithm (algorithm 3). Despite a PPV of only 56.6%, sensitivity was 88.3%, which was notably better than either algorithm alone. The first algorithm included a combination of diagnosis codes with codes for various procedures or drugs, typically on the same day. Alternatively, two diagnosis codes could occur within 12 months of one another after a diagnostic procedure with biopsy. The second algorithm required two or more lymphoma diagnosis codes within two months. The requirement of only one diagnosis code led to an unacceptable PPV. Thus, it is recommended that a single diagnosis code alone not be used to identify lymphoma. Finally, this study was limited in that it used only registry-identified cases as true positives, so the performance characteristics reported are dependent on the ability of the registry to identify all cases. This has been brought into question, particularly for less common cancers. The PPVs of the algorithms would be higher if cases not confirmed by the registry were confirmed by medical record review.

Given that only one validation study of lymphoma was identified, it focused on an older population in one state, and it considered only registry identified cases as true positives, opportunities for studying the validity of administrative data-based lymphoma definitions are many. Future research might include examining the validity of algorithms in multiple geographic settings, inclusion of plasma cell diseases, and among a broader range of ages. It is also recommended that a hybrid design be considered for future validation studies. This would involve accepting registry-confirmed cases as true positives, and conducting medical record reviews for those algorithm-identified cases that were not confirmed by the registry. This design could be more efficient than a study that requires medical record review of all cases to be validated, though it would be dependent upon linkage of the administrative data source to a cancer registry.

II. PROJECT OBJECTIVES

The primary objective of this project was to identify studies that have validated algorithms used to identify various health outcomes of interest (HOIs) using administrative data from the United States or Canada, and to summarize the results of those validation studies. If fewer than five validation studies were identified, a secondary objective was to identify non-validated algorithms that have been used to identify the HOIs using administrative data.

III. BACKGROUND

The U.S. Food and Drug Administration (FDA) Mini-Sentinel contract is a pilot program that aims to conduct active surveillance to detect and refine safety signals that emerge for marketed medical products. In order to perform this work, the program needed to identify algorithms used to detect various health outcomes of interest using administrative data sources and identify the performance characteristics of these algorithms as measured in the studies in which they were used. The data sources of interest were limited to those from the United States or Canada to increase their relevance to the Mini-Sentinel data sources, which are all from the United States. The Mini-Sentinel Protocol Core developed a preliminary list of approximately 140 potential health outcomes of interest, based on several criteria. These criteria included: 1) previous validation studies had been identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies[12], 2) a list of designated medical events from a proposed FDA rule on the safety reporting requirements for

human drug and biological products[13], 3) the Observational Medical Outcomes Partnership (OMOP)[12] had commissioned reports on algorithms used to identify the health outcome using administrative data.[14]

From the original list of 140 HOIs, the Protocol Core worked with FDA to select 20 for which reviews of algorithms would be completed. HOIs for which OMOP had already commissioned reports were purposefully excluded in order to avoid duplication of effort.

Lymphoma was one of the 20 HOIs selected for review. This report describes the review process and findings for the lymphoma definition algorithms.

IV. METHODS

A. SEARCH STRATEGY

The general search strategy was developed based on prior work by OMOP and its contractors, and modified slightly for these reports. Originally, OMOP contracted with two organizations to perform reviews of 10 HOIs. Because the search strategies used by each organization resulted in very different sets of articles, OMOP investigators reviewed the PubMed indexing of the articles deemed useful in final reports and developed a strategy that would identify the majority of these citations while maintaining efficiency in the number of abstracts that would need to be reviewed. Mini-Sentinel investigators made minor changes to this strategy that would result in the identification of more citations, and confirmed empirically that the majority of relevant articles from one set of OMOP reports (angioedema)[15,16] would be identified using this approach. The base search strategy was then combined with PubMed terms representing the HOIs. Medical subject heading (MeSH) terms were generally preferred as HOI search terms due to their likely specificity. Text word searches were sometimes used, particularly when the MeSH search resulted in a small number of citations for review. The workgroup also searched the database of the Iowa Drug Information Service (IDIS) using a similar search strategy to identify other relevant articles that were not found in the PubMed search. For a limited number of outcomes where very few citations were identified from PubMed and IDIS searches, Embase searches were conducted. Search results were restricted to articles published on or after January 1, 1990.

University of Iowa investigators compiled the search results from different databases and eliminated duplicate results using a citation manager program. The results were then output into two sets of files, one containing the abstracts for review and the other for documenting abstract review results.

The search strategy and results for lymphoma are detailed in the Results section. The PubMed search was conducted on June 23, 2010, and the IDIS searches on June 23, 2010.

B. ABSTRACT REVIEW

1. Abstract Review Methods

Each abstract was reviewed independently by two investigators to determine whether the full-text article should be reviewed. Exclusion criteria were documented sequentially (i.e. if exclusion criterion 1 was met then the other criteria were not documented). If the reviewers disagreed on whether the full-text should be reviewed, then it was selected for review. Inter-rater agreement on whether to include or exclude an abstract was calculated using a Cohen's kappa statistic. The goal was to review any

administrative database study that used data from the United States or Canada and studied the HOI. Because validation components of studies are not necessarily included in the abstract and other relevant citations might be identified from the references of such studies the absence of validation methods was not a criteria used in screening abstracts.

2. Abstract Exclusion Criteria

1. Did not study the HOI.
2. Not an administrative database study. Eligible sources included insurance claims databases as well as other secondary databases that identify health outcomes using billing codes.
3. Data source not from the United States or Canada.

C. FULL-TEXT REVIEW

1. Full-Text Review Methods

Full-text articles were reviewed independently by two investigators, with a goal of identifying validation studies described in the article itself or from the reference section of the article. Citations from the article's references were selected for full-text review if they were cited as a source for the HOI algorithm, or were otherwise deemed likely to be relevant. Full-text review exclusion criteria were applied sequentially, since if fewer than 5 validation studies were identified, up to 10 of the articles excluded based on the second criterion would need to be incorporated into the final report. If there was disagreement on whether a study should be included, the two reviewers attempted to reach consensus on inclusion by discussion. If the reviewers could not agree, a third investigator would be consulted to make the final the decision.

2. Full-Text Exclusion Criteria

The previous exclusion criteria were still used along with two additional:

1. Poorly described HOI identification algorithm that would be difficult to operationalize.
2. No validation of outcome definition or reporting of validity statistics.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators were surveyed to request information on any published or unpublished studies that validated an algorithm to identify an HOI in administrative data. Studies that would not be excluded by one of the aforementioned criteria were included in the final report.

E. EVIDENCE TABLE CREATION

A single investigator abstracted each study for the final evidence table. The data included in the table were confirmed by a second investigator for accuracy.

F. CLINICIAN OR TOPIC-EXPERT CONSULTATION

A clinician or topic-expert was consulted to review the results of the evidence table and discuss how they compare and contrast to diagnostic methods currently used in clinical practice. This included whether certain diagnosis codes used in clinical practice were missing from the algorithms, and the appropriateness of the validation definitions compared to diagnostic criteria currently used in clinical practice. A summary of this consultation was included in the results.

V. RESULTS

A. SEARCH STRATEGY AND RESULTS

The following summarizes the search results obtained from PubMed and IDIS searches. The PubMed search identified 700 citations (Table 1), and the IDIS searches identified 24 citations (Table 2). The total number of unique citations from the combined searches was 713.

Table 1. Pubmed Search Strategy and Results: Performed 6/23/10

Search	Query	Results
#1	("Pharmaceutical preparations/adverse effects"[Mesh] OR "Pharmaceutical preparations/contraindications"[Mesh] OR "Pharmaceutical preparations/poisoning"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical preparations/toxicity"[Mesh] OR "Pharmaceutical preparations/therapy"[Mesh] OR "Pharmaceutical preparations/analysis"[Mesh] OR "Chemical actions and uses/adverse effects"[Mesh] OR "Chemical actions and uses/contraindications"[Mesh] OR "Chemical actions and uses/poisoning"[Mesh] OR "Chemical actions and uses/therapeutic use"[Mesh] OR "Chemical actions and uses/toxicity"[Mesh] OR "Chemical actions and uses/therapy"[Mesh] OR "Chemical actions and uses/analysis"[Mesh] OR "Chemical actions and uses/epidemiology"[Mesh] OR "Drug toxicity"[Mesh] OR "Diseases Category/chemically induced"[Mesh] OR "Diseases Category/drug therapy"[Mesh] OR "Diseases Category/epidemiology"[Mesh] OR "Validation Studies"[pt] OR "Validation Studies as Topic"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR “Predictive Value”[tw]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	1863979
#2	("Premier"[All] OR "Solucient"[All] OR "Cerner"[All] OR "Ingenix"[All] OR "LabRx"[All] OR "IHCIS"[All] OR "marketscan"[All] OR "market scan"[All] OR "Medstat"[All] OR "Thomson"[All] OR "pharmetrics"[All] OR "healthcore"[All] OR "united healthcare"[All] OR "UnitedHealthcare"[All] OR "UHC"[All] OR "Research Database"[All] OR "Group Health"[All] OR "HCUP"[All] OR ("Healthcare Cost"[All] AND "Utilization Project"[All]) OR ("Health Care Cost"[All] AND "Utilization Project"[All]) OR "MEPS"[All] OR "Medical Expenditure Panel Survey"[All] OR "NAMCS"[All] OR "National Hospital Ambulatory Medical Care Survey"[All] OR "National Ambulatory Medical Care Survey"[All] OR "NHIS"[All] OR "National Health Interview Survey"[All] OR "Kaiser"[All] OR "HMO Research"[All] OR "Health Maintenance Organization"[All] OR "HMO"[All] OR "Cleveland Clinic"[All] OR "Lovelace"[All] OR "Department of Defense"[All] OR "Henry Ford"[All] OR "i3 Drug Safety"[All] OR "i3"[All] OR "Aetna"[All] OR "Humana"[All] OR "Wellpoint"[All] OR "IMS"[All] OR "Intercontinental Marketing Services"[All] OR "IMS Health"[All] OR "Geisinger"[All] OR "GE Healthcare"[All] OR "MQIC"[All] OR "PHARMO"[All] OR "Institute for Drug Outcome Research"[All] OR "Pilgrim"[All] OR "Puget Sound"[All] OR "Regenstrief"[All] OR "Saskatchewan"[All] OR "Tayside"[All] OR "MEMO"[All] OR "Veterans Affairs"[All] OR "Partners Healthcare"[All] OR "Mayo Clinic"[All] OR "Rochester Epidemiology"[All] OR "Indiana Health Information Exchange"[All] OR "Indiana Health"[All] OR "Intermountain"[All] OR "blue cross"[All] OR	373522

	"health partners"[All] OR "health plan"[All] OR "health services"[All] OR "Nationwide Inpatient Sample"[All] OR "National Inpatient Sample"[All] OR "medicaid"[All] OR "medicare"[All] OR "MediPlus"[All] OR "Outcome Assessment"[All] OR "insurance database"[All] OR "insurance databases"[All] OR "Data Warehouse"[All] OR "ICD-9"[All] OR "international statistical classification"[All] OR "international classification of diseases"[All] OR "ICD-10"[All] OR "Database Management Systems"[Mesh] OR "Medical Records Systems, Computerized"[Mesh] OR "CPT"[All] OR "Current procedural terminology"[All] OR "drug surveillance"[All] OR ("claims"[tw] AND "administrative"[tw]) OR ("data"[tw] AND "administrative"[tw]) OR "Databases, Factual"[Mesh] OR "Databases as topic"[Mesh] OR "Medical Record Linkage"[Mesh] OR "ICD-9-CM"[All Fields] OR "ICD-10-CM"[All Fields] OR (TennCare [tiab]) OR (RAMQ [tiab]) OR (Cigna [tiab]) OR ((british columbia[tiab]) AND ((health[tiab]) OR (data[tiab]) OR (database[tiab]) OR (population[tiab]))) OR (CIHI [All Fields]) OR ((manitoba[tiab]) AND ((center for health policy[all fields]) OR (population[tiab]) OR (health insurance[tiab]))) OR ((ontario[tiab]) AND ((population[tiab]) OR (OHIP[tiab]) OR (registered persons database[tiab]) OR (health insurance [tiab]) OR (ICES[All Fields]) OR (Institute for Clinical Evaluative Sciences[All Fields]))) OR ((Alberta[tiab]) AND ((health[tiab]) OR (data[tiab]) OR (database[tiab]) OR (population[tiab]) OR (Alberta Health and Wellness[All Fields]))) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	
#3	Search #1 and #2 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	109667
#4	("Editorial"[pt] OR "Letter"[pt] OR "Meta-Analysis"[pt] OR "Randomized Controlled Trial"[pt] OR "Clinical Trial, Phase I"[pt] OR "Clinical Trial, Phase II"[pt] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trial, Phase IV"[pt] OR "Comment"[pt] OR "Controlled Clinical Trial"[pt] OR "case reports"[pt] OR "Clinical Trials as Topic"[Mesh] OR "double-blind"[All] OR "placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh] OR "Review"[pt] OR "Prospective Studies"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	2603891
#5	Search #3 not #4 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	69952
#6	Search "lymphoma"[Mesh] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	55530
#7	Search "lymphoma"[All Fields] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	77166
#8	Search #6 or #7 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	82392
#9	Search #5 and #8 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	700

Table 2. IDIS Search Strategy and Results: Performed 6-23-10

ADVANCED SEARCH

All Fields:

("Premier" OR "Solucient" OR "Cerner" OR "Ingenix" OR "LabRx" OR "IHCIS" OR "marketscan" OR "market scan" OR "Medstat" OR "Thomson" OR "pharmetrics" OR "healthcore" OR "united healthcare" OR "UnitedHealthcare" OR "UHC" OR "Research Database" OR "Group Health" OR "HCUP" OR ("Healthcare Cost" AND "Utilization Project") OR ("Health Care Cost" AND "Utilization Project") OR "MEPS" OR "Medical Expenditure Panel Survey" OR "NAMCS" OR "National Hospital Ambulatory Medical Care Survey" OR "National Ambulatory Medical Care Survey" OR "NHIS" OR "National Health Interview Survey" OR "Kaiser" OR "HMO Research" OR "Health Maintenance Organization" OR "HMO" OR "Cleveland Clinic" OR "Lovelace" OR "Department of Defense" OR "Henry Ford" OR "i3 Drug Safety" OR "i3" OR "Aetna" OR "Humana" OR "Wellpoint" OR "IMS" OR "Intercontinental Marketing Services" OR "IMS Health" OR "Geisinger" OR "GE Healthcare" OR "MQIC" OR "PHARMO" OR "Institute for Drug Outcome Research" OR "Pilgrim" OR "Puget Sound" OR "Regenstrief" OR "Saskatchewan" OR "Tayside" OR "MEMO" OR "Medicines Monitoring Unit" OR "Veterans Affairs" OR "Partners Healthcare" OR "Mayo Clinic" OR "Rochester Epidemiology" OR "Indiana Health Information Exchange" OR "Indiana Health" OR "Intermountain" OR "blue cross" OR "health partners" OR "health plan" OR "health services" OR "Nationwide Inpatient Sample" OR "National Inpatient Sample" OR "medicaid" OR "medicare" OR "MediPlus" OR "Outcome Assessment" OR "insurance database" OR "insurance databases" OR "Data Warehouse" OR "ICD-9" OR "international statistical classification" OR "international classification of diseases" OR "ICD-10" OR "Database Management Systems" OR "Medical Records Systems, Computerized" OR "CPT" OR "Current procedural terminology" OR "drug surveillance" OR ("claims" AND "administrative") OR ("data" AND "administrative") OR "Databases, Factual" OR "Databases as topic" OR "Medical Record Linkage" OR "ICD-9-CM" OR "ICD-10-CM" OR "TennCare" OR "RAMQ" OR "Cigna" OR "British Columbia" OR "CIHI" OR "Manitoba" OR "Ontario" OR "Alberta")

AND **Disease(s):**

200.* or 202.* or 201.*

AND NOT **Descriptor(s):**

("CASE REPORT ADULT 0" or "CASE REPORT PEDIATRIC 1" or "CASE REPORT GERIATRIC 2" or "REVIEW ADULT 6" or "STUDY NON-CLINICAL 8" or "REVIEW PEDIATRIC 21" or "REVIEW GERIATRIC 23" or "STUDY RANDOMIZE ADULT 135" or "STUDY RANDOMIZE PEDIATRIC 136" or "STUDY RANDOMIZE GERIATRIC 137" or "CROSS-OVER 144" or "META-ANALYSIS 145" or "N-OF-ONE TRIAL 146" or "PRACTICE GUIDELINE 156" or "SYSTEMATIC REVIEW 161" or "ANNOTATED BIBLIOGRAPHY 167" or "PRIORITY CLIN PRACT GUIDE 168") or ("FDA APPROVAL PACKAGE 155")

AND NOT **Author(s):**

"(editorial)" or "(Letter to Ed)"

Years: 1990-2010

Records = 24

B. ABSTRACT REVIEWS

The two searches resulted in 700 plus 24 articles and there were 11 duplicates, resulting in 713 unique articles. Of the 713 abstracts reviewed, 311 were selected for full-text review; 223 were excluded because they did not study lymphoma, 64 were excluded because they were not administrative database studies, and 115 were excluded because the data source was not from the United States or Canada. Cohen's kappa for agreement between reviewers on inclusion vs exclusion of abstracts was 0.61.

C. FULL-TEXT REVIEWS

The 311 full-text articles reviewed identified 1 study in the final evidence table that showed validation and 10 studies were included that had used an administrative database, but no validation was reported; 115 were excluded because the lymphoma identification algorithm was poorly defined, and no additional studies were excluded because they included no validation of the outcome definition or reporting of validity statistics other than the 10 summarized in Table 4. There were an additional 79 studies eliminated because the study outcome was not lymphoma, 87 more did not use an administrative database and 19 studies were not conducted in the United States or Canada. Reviewers identified no additional citations for review from full-text article references. Cohen's kappa for agreement between reviewers on inclusion vs exclusion of full-text articles reviewed was 0.75. It should be noted that the initial full-text review process selected a larger number of manuscripts for inclusion. However, an adjudication process was conducted which excluded the majority of the originally selected studies that validated registry cases but did not include administrative data of the kind captured through billing claims, as was the intended focus of the report. The one validation study, by Setoguchi , Solomon, Glynn, Cook, Levin, and Schneeweiss,[1]] was the only validation study selected for inclusion after the adjudication process. Algorithm details were obtained from the authors. Ten studies of non-validated algorithms were also included since only one validation study was identified.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators provided no published and no unpublished reports of validation studies that had been completed by their teams.

E. EVIDENCE INCLUDED IN TABLE

The 1 study included in the evidence table, Table 3, was identified from the initial search strategy, none were identified through references of articles that underwent full-text review, and none were provided by Mini-Sentinel Investigators. The 10 studies in the table with non-validated algorithms, Table 4, were all identified by the initial search strategy, but only 3 were correctly classified as only lacking validation. The other 7 were identified during the adjudication process. A complete list of studies with clear HOI definitions that were eligible to be selected for inclusion is available in Appendix B.

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

Codes Used in Algorithms. The validated algorithm for this health outcome of interest used International Classification of Disease-Clinical Modification (ICD-9-CM) codes, clinical procedural terminology (CPT) codes, and codes for the receipt of various chemotherapies.[1] All of the lymphoma codes, provided to us by the study authors, are summarized in Appendix C. Setoguchi, et al.[1] evaluated four different algorithms:

- Definition 1: Combination of diagnosis and procedures on the same day or within the same hospitalization, so any of the following:
    - 1 or more cancer diagnosis + any diagnosis or procedure codes related to complications of cancer or palliative care in two weeks followed by another diagnosis of cancer within 12 months

  - 1 or more diagnostic procedure with biopsy followed by 2 or more cancer diagnoses at two different occasions within 12 months (recorded on different dates from the procedures)
  - 1 or more cancer diagnosis + any surgery related to cancer during the same hospitalization and/or visit
  - 1 or more cancer diagnosis + any cancer chemotherapy during the same hospitalization and/or visit
  - 1 or more cancer diagnosis + any radiation therapy during the same hospitalization and/or visit
  - 1 or more cancer diagnosis + hematopoietic cell transplantation during the same hospitalization and/or visit (for leukemia only)
  - 1 or more cancer diagnosis + oral chemotherapy dispensing within 2 weeks after the diagnosis
- Definition 2: Two diagnosis codes of cancer within 2 months
- Definition 3: Cases defined by Definition 1 or Definition 2
- Definition 4: One or more diagnosis codes for cancer

The studies done in administrative databases that did not report validations all used ICD-CM diagnosis codes only. Three of the studies used ICD-8-CM codes; five studies used ICD-9-CM diagnosis codes. One of the challenges that two studies faced was that the databases spanned a broad range of years and the coding scheme sometimes changed, so one study used ICD-8-CM and ICD-9-CM codes and another one used ICD-9-CM and ICD-10-CM diagnosis codes.

Validation Criteria and Methods. Setoguchi, et al.,[1] identified patients over 65 years of age from the Medicare Claims database Pharmaceutical Assistance for the Elderly (PACE) in Pennsylvania (PA). Patients identified by the ICD-9 diagnosis codes and/or CPT codes were then linked to the PA cancer registry to validate the lymphoma diagnosis. They report that patients identified with lymphoma were confirmed by microscopic pathology in 87.6% of the cases, laboratory test in 5.9% of the cases, radiographic or other imaging in 1.4% of the cases, by clinical diagnosis only in 1.6% of the cases and by other means in 3.5% of the cases.

Validation Algorithms. Setoguchi, et al.[1] evaluated four different algorithms in their study. Algorithm 1 used a combination of diagnosis and procedures on the same day or within the same hospitalization. With this approach they had the fewest number of cases, 564, the best specificity (99.86%) and a positive predictive value (PPV) of 61.52%. The sensitivity of algorithm 1 was 55.17%. Algorithm 2 required only two diagnosis codes appearing within two months. This increased the number of cases identified (n=799). Specificity fell slightly to 99.81%, sensitivity improved to 79.81%, and the PPV increased to 62.83%. Algorithm 3 considered a person a case if they met the criteria for either algorithm 1 or algorithm 2. This did further increase the number of cases (n=926) but specificity fell further to 99.74% and PPV dropped to 56.59%. Despite the decrease in PPV, the authors described this as their preferred algorithm, largely because sensitivity increased to 88.31% and specificity was not substantially impacted due to the rarity of the outcome. The fourth algorithm evaluated was the least stringent, requiring the presence of only one new diagnosis code for lymphoma. This resulted in the most cases (n=1607), but specificity fell to 99.33% and PPV went to the lowest value of 34.72% and sensitivity increased to 88.71%. All four algorithms had reasonable specificity (> 99%), but it would seem that definition 2 with two diagnosis codes recorded within two months had the best PPV while also having a reasonable sensitivity.

Selected Patient Populations and Population Characteristics. The validation study focused on the Medicare population, patients over 65 with a mean age of 80.8 years and where only 21.6% were males.[1] Among the non-validated studies, two other studies also focused on Medicare patients where all subjects were over 65.[6,9] One of these[6] and two others[3,10] focused on patients with end stage renal disease who were on a transplant list or had just received transplants. Here patient ages spanned the entire age spectrum and there was a near balance in males and females. Four studies[4,5,7,8] were done in the Veterans Administration system; two were looking at lymphoma rates during the Vietnam era[4,5], one looked at lymphoma rates in general[8] and the other focused on lymphoma associated with HIV[7]. One study was done using a hospital database in Canada where lymphoma was assessed from a comorbidity perspective with irritable bowel disease.[2]

Time Period of Data Collection. The studies were published form 1991 to 2008, but time frame covered by the databases spanned from 1965 through 2006. The validation study examined data from 1997-2000.

Incident vs Prevalent Outcome Validation. The validation study[1] focused on new cancer diagnosis and all of the non-validated studies identified focused on the assessment of new cases of lymphoma[2-10] except one which focused on lymphoma as a cause of death[11].

Principal vs Secondary Diagnosis. Occasionally the lymphoma was assessed as a comorbidity[2,3,6,7,10], but in most cases it was the primary diagnosis[1,4,5,8,9,11]. The validation study did not place restrictions on the position of the code.

Patient Setting. Most of the studies included in the two tables did not specify a particular setting. The databases generally incorporated both hospitalized and outpatient data so diagnosis code screening was acceptable from either setting.

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

Generally there were not a lot of restrictions when identifying this health outcome of interest. The one validation study identified examined Medicare enrollees at least 65 years of age who were part of Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE). They were required to be enrolled and have no cancer-related claims for 6 months prior to January 1, 2007, the beginning of the study period.

H. EVIDENCE TABLES

Table 3. Positive Predictive Values by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure, Operational Definition, and Validation Statistics
Setoguchi et al. 2007[1]	Health care utilization data were derived from Medicare claims data linked to pharmacy dispensing data from the Pharmaceutical Assistance Contract for the Elderly (PACE) in Pennsylvania between 1 January 1997 and 31 December 2000. The gold standard cancer information was Pennsylvania State (PA) Cancer Registry data from 1 January 1989 to 31 December 2000. Lymphoma patients identified (n-629) were 21.6% male, were 65 years and older with a mean age of 80.8 (SD 6.5) years.	Incident cancer cases identified in the administrative database which were then linked to the PA cancer registry to validate the diagnosis.	Claims data-based definitions of incident cancer using (a.) ICD-9 diagnosis codes, (b.) Current Procedural Terminology (CPT) codes for screening procedures, surgical procedures, radiation therapy, chemotherapy, and nuclear medicine procedures, and/or (c.) National Drug Code (NDC) prescription codes for medications used for cancer treatment available in PACE. Four different algorithms were evaluated: **Algorithm 1:** one or more ICD-9 diagnosis codes for lymphoma plus any procedure code related to complications of cancer within two weeks of the diagnosis plus another cancer diagnosis code within 12 months; or 1 diagnostic procedure with biopsy followed by 2 or more cancer diagnosis codes at two different occasions within 12 months (recorded on different dates from the procedures); or 1 cancer diagnosis + any surgery related to cancer during the same hospitalization and/or visit. Or 1 cancer diagnosis + any cancer chemotherapy during the same hospitalization and/or visit; or 1 cancer diagnosis + any radiation therapy during the same hospitalization and/or visit; or 1 cancer diagnosis + hematopoietic cell transplantation during the same hospitalization and/or visit (for leukemia only); or 1 cancer diagnosis + oral chemotherapy dispensing within 2 weeks after the diagnosis. **Algorithm 2:** 2 or more diagnoses of cancer (ICD-9 codes) within 2 months	Claims data was linked to the cancer registry to confirm diagnosis. Microscopic diagnosis was reported in 87.6% of the cases, laboratory test in 5.9% of cases, radiographic or other imaging (1.4%), clinical diagnosis (1.6%) and unknown (3.5%). When the ICD-9 diagnosis codes and current procedure terminology codes (CPT) were used for lymphoma according to **algorithm 1,** 564 cases were identified with a sensitivity of 55.17%, a specificity of 99.86% and a positive predictive value (PPV) of 61.52%. When **algorithm 2** was used, which required two ICD-9 diagnosis codes within two months, there were 799 cases identified with a sensitivity of 79.81%, a specificity of 99.81% and a PPV of 62.83%. **Algorithm 3**, which identified cases meeting criteria for algorithm 1 or algorithm 2, identified 926 cases with a sensitivity of 88.31%, a specificity of 99.74% and a PPV of 56.59%. **Algorithm 4,** which only required the presence of one ICD-9 diagnosis code, identified 1607 cases with 88.71% sensitivity, 99.33% specificity and a PPV of 34.72%. The ICD-9 diagnosis codes and clinical procedure codes can identify incident hematologic malignancies and solid tumors with high specificity but with relatively low to moderate sensitivity and positive predictive values (PPVs). Within the cases identified by both the registry and

			Algorithm 3: Cases defined by using algorithm definition 1 or 2 **Algorithm 4:** 1 or more diagnosis codes for cancer (ICD-9 codes) *Specific codes utilized to identify lymphoma included:* Lymphoma ICD-9-CM diagnosis codes: 200.XX, 201.XX, 202.XX (Except 202.5X and 202.6X) ICD-9 and CPT codes for complications: *Hypercalcemia:* ICD-9 codes 275.40, 275.42, or 275.49 *Spinal cord compression:* ICD-9 code 198.3 or 336.9 *Superior vena cava syndrome:* ICD-9 code 459.2 *Pain management or palliative care:* CPT code 99551 or 99552 CPT codes for diagnostic procedures with biopsy: 38500, 38505, 38510, 38520, 38525, 38530, 38542, 49180, 76003, 76360, 76365, 76942, 88170, 88171, 88172, 88173, 85095, 85097, 85102, 38220, 38221, 38100, 38101, 38102, 38115, 38589, 38562, 38564, 38570, 61332, 54550, 54505, 54512, 54520, 54530, 19100, 19101, 19102, 42826, 11100, 11101 CPT codes for cancer chemotherapies: 36640, 51720, 96400, 96405, 96406, 96408, 96410, 96412, 96414, 96420, 96422, 96423, 96425, 96440, 96445, 96450, 96500, 96501, 96504, 96505, 96508, 96510, 96511, 96512, 96520, 96524, 96530, 96538, 96540, 96542, 96545, 96549, 96450, 99555 CPT codes for cancer-related radiations: 77261, 77262, 77263, 77280,	the claims-based definition, the agreement in the first dates of cancer diagnosis was sufficient. Most cases were identified in claims within 2 weeks of the diagnosis, though the claim was often later than the diagnosis. The authors also examined the bias that would result from the less than optimal PPV, using algorithm 3. The claims-based definition resulted in relatively small bias in the example of a typical pharmacoepidemiologic study with drug A possibly causing lymphoma. Finally, the authors noted that registries may not capture all cancers, so the gold standard in this study is limited compared to a medical record review of every identified case. Limitations of case ascertainment methods may be more significant for less common cancers such as lymphoma compared to others such as breast or prostate cancer.

			77285, 77290, 77295, 77299, 77300, 77305, 77310, 77315, 77321, 77326, 77327, 77328, 77331, 77332, 77333, 77334, 77336, 77370, 77399, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77417, 77419, 77420, 77425, 77430, 77431, 77432, 77470, 77499, 76960, 55859, 55860, 55862, 55865, 77750, 77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77789, 77790, 77799, 79200, 79300, 79400, 79420, 79440, 79900, 79999 CPT codes for hematopoietic transplantations: 38230, 38231, 38240, 38241, 38242	

Table 4. Non-Validated Algorithms

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm
Bernstein & Nabalamba 2007[2]	Hospitalization data from Statistics Canada Health Person Oriented Information hospital database (1994/1995 to 2003/2004). Patients with irritable bowel disease in the study period were 47,000.	The database was first scanned to identify patients with irritable bowel disease, and this subset was then scanned to identify new onset of lymphoma and other comorbidities.	Non-Hodgkin's lymphoma (ICD-9: 200.x or ICD-10-CA: C83.2, C83.3, C83.4, C83.5, C83.7, C96.3 and C88.08), Hodgkin's disease (ICD-9: 201.x or ICD-10-CA: C81)
Caillard et al. 2006[3]	Medicare data was evaluated from the United States Renal Data System for patients who had received a renal transplant from January 1992 through July 2000. A total of 66,159 kidney recipients were included in the analysis. Lymphoid proliferations were diagnosed in 1169 patients (1.8%): 823 (1.6%) were reported as non Hodgkin lymphoma, 160 (0.24%) as myeloma, 60 (0.1%) as Hodgkin disease, and 126 (0.19%) as lymphoid leukemia. Mean age for each of those groups was 45.4, 46.2, 52.4, 47.3 and 48.3 years respectively. Gender ranged from	To analyze the Medicare claims with a new diagnosis of lymphoid disorders occurring after transplantation	ICD-9-CM diagnosis codes: non Hodgkin's lymphomas: 200.x and 202.x, Hodgkin diseases: 201.x, myelomas: 203.x, lymphoid leukemias: 204.x.

	55-67% male for each group.		
Dalager et al. 1991[4]	VA National Administrative data on Vietnam-era veterans born between 1937 and 1954. There were 201 non-Hodgkin's lymphomas (NHL) cases and 358 controls that served in the military from July 1965 to March 1973.	New onset of histology confirmed non-Hodgkin's lymphoma.	ICD-8 codes 200.x or 202.x
Dalager et al. 1995[5]	VA National Administrative data on Vietnam-era veterans born between 1937 and 1954. There were 283 Hodgkin's lymphomas (HL) cases and 404 controls that served in the military from July 1965 to March 1973.	New onset of histology confirmed Hodgkin's lymphoma.	ICD-8 codes 201.x
Kasiske et al. 2004[6]	The Medicare enrollment database was searched to determine Medicare Part A and Part B primary pay status along with coverage start and stop dates. There were 35,765 (47%) fulfilling these criteria out of a total of 76,467 first transplantations between 1995 and 2001. Patient demographics were not provided.	First-time recipients of deceased or living donor kidney transplantations were evaluated for a new onset of cancer.	ICD-9-CM codes used to identify specific cancers: Lymphoma 200.x, 202.x, 204.x Hodgkin's 201.x Myeloma 203.x Leukemia 205.x, 206.x, 207.x, 208.x All other cancers and their codes are summarized in the Appendix of the article.
McGinnis et al. 2006[7]	VA National Administrative data on inpatient files from October 1990 and in outpatient files from October 1996 through September 2004 were used to identify 197 HIV positive NHL patients and 43 HIV negative NHL patients.	First diagnosis of NHL in HIV positive patients.	ICD-9-CM site-specific cancer codes as identified by Surveillance Epidemiology and End Results (SEER) for hepatocellular carcinoma: 152.0, 155.2; and for NHL: 200.0 to 200.8, 202.0 to 202.2, and 202.8 to 202.9.22. Cancers were included if the veteran had one or more inpatient or two or more outpatient cancer diagnoses of the same type. This approach was previously validated with the HIV algorithm, but not with the NHL algorithm.
Namboodiri et al. 1991[8]	VA National Administrative data on veterans 20 years and older were evaluated for the period 1970 to 1982. The population was predominantly male and ages ranged from 20 to over 84 years.	The neoplasms that were examined included first onset of Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma and leukemia.	Authors report studying a subset of patients with ICD codes of 200.x to 208.x to capture these outcomes. The coding changed from ICD-8 to ICD-9 during this period, and the authors describe using a table that compared codes to classify these outcomes. No information on specific codes for specific conditions was provided.
Shea et al. 2008[9]	Patients were Medicare beneficiaries with claims from the Centers for Medicare & Medicaid Services for the period 2003	Incident breast cancer, colorectal cancer, leukemia, lung cancer, or	ICD-9-CM diagnosis codes for lymphoma included: 200.00-200.88, 202.00-202.28, 202.80-202.98, V10.71, and V10.79 and leukemia included: 202.40-202.48,

	through 2006. The mean age of patients was 75 years and there was no significant difference in the number of males compared to females.	lymphoma who received chemotherapy in inpatient hospital, institutional outpatient, or physician office settings.	203.10, 204.00, 204.10, 204.20, 204.80, 204.90, 205.00, 205.10, 205.20, 205.80, 205.90, 206.00, 206.10, 206.20, 206.80, 206.90, 207.00, 207.10, 207.20, 207.80, 208.00, 208.10, 208.20, 208.80, 208.90, V10.60-V10.63, and V10.69.
Smith et al. 2006[10]	Data from the United States Renal Data System (USRDS) for end stage renal disease patients that were placed on the transplant waiting list from January 1990 through December 1999. There were 357 cases of lymphoma (64.4% males) over 107,298 follow-up years. The highest rates occurred in Caucasian males.	New onset of lymphoma with the first hospitalization with lymphoma diagnosis following transplantation or placement on the transplant waiting list as the date of onset.	ICD-9-CM codes consistent with a diagnosis of lymphoma. Hospitalizations with a primary or secondary diagnosis code of 200–208 or 238.7 were considered hospitalizations for lymphoma. Note: the authors used this set of codes, but it also contains many leukemia codes which are not appropriate for lymphoma identification.
Watanabe et al. 1991[11]	Administrative records from the VA Beneficiary Identification and Record Locator Subsystem was used to identify Vietnam era veterans that had died between July 4, 1965 and June 30, 1982 and whose military service ended after 1965 and started before 1973. There were 140 army and 42 marine Non-Hodgkin's lymphoma deaths and 116 army and 25 Hodgkin's lymphoma deaths.	Cause specific numbers of deaths	ICD-8-CM codes of 200 or 202 for Non-Hodgkin's lymphoma and 201 for Hodgkin's lymphoma.

I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

Characterizing algorithms for lymphoma as an HOI is complicated from the beginning by the lack of uniformity in definitions of lymphoma. Primary lymphoid malignancies would be a term to broadly embrace the diseases of: nodal or tumor forming lymphomas (Hodgkin Lymphoma and others); primarily blood-borne lymphoid leukemias (chronic or acute), and plasma cell disorders (amyloidosis, Huppert's disease, or multiple myeloma). By convention, the plasma cell disorders would very commonly be excluded from discussions of "lymphoma", and the Setoguchi, et al. paper indeed excluded ICD-9 code 203.xx (personal communication). The lymphoid leukemias are categorized less consistently. The disease characterized by a clonal proliferation of B-cells co-expressing surface molecules CD5, CD19, and CD23 (ICD 204.xx), is arbitrarily referred to by clinicians as either "chronic lymphocytic *leukemia* or small lymphocytic *lymphoma* often based upon a predominantly nodal or blood-borne presentation, is officially referred to by World Health Organization (WHO) as chronic lymphocytic leukemia/small lymphocytic lymphoma in all cases, and is classified as lymphoma but not leukemia by WHO but as leukemia and not lymphoma by SEER (and Setoguchi). Similarly lymphoblastic lymphoma/leukemia would generally be called leukemia by clinicians and SEER, but is a lymphoma according to the World Health Organization (WHO). Thus all published studies need to carefully report definitions of "lymphoma" used in the relevant data-bases, registries and resulting algorithms.

A second peril to optimizing sensitivity and specificity of lymphoma capture in these described algorithms is the unfortunate use of historical terms for lymphoid diseases that were recognized as medical conditions and named before they were recognized as lymphomas. Examples (with WHO terminology) include Waldenstrom's macroglobulinemia (lymphoplasmacytic lymphoma), gastric or orbital MALT (extra-nodal marginal zone lymphoma), mycosis fungoides (cutaneous T-cell lymphoma), lymphomatoid granulomatosis (angiocentric pulmonary B-cell lymphoma) and large granular lymphocytosis (T-cell granular lymphocytic leukemia). Although each of the above represents a relatively uncommon form of lymphoma, in aggregate they account for 5-10% of lymphomas.

Setoguchi and co-authors offer the lack of complete capture of diseases by cancer registries as a possible explanation for low PPV. This possibility seems especially relevant in the case of lymphoma where many subtypes are diagnosed on the basis of clinical findings or blood tests and not captured on a pathologic biopsy which is the most efficient way for registries to identify cases. Examples include chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, primary cutaneous T-cell lymphomas, T-cell granular lymphocytic leukemia, and vitreoretinal lymphoma. Notably this is complicated by the significant overlap with diseases above that retain older, non-malignant sounding clinical terminology. Thus, it seems likely that PPV of the described algorithms may well vary some across registries as capture completeness of these subtypes is likely operator-dependent.

Although subtle evolution in the subclassification of lymphomas is frequent and common, only a more recent change in disease definition is worth mentioning as having potentially important impact. Chronic lymphocytic leukemia/small lymphocytic lymphoma has historically included any detectable population of clonal CD5, CD19, and CD23 expressing B-cells. In 2008, however the definition was limited to include only patients with at least 5,000 such cells per microliter of blood, and classifying those with fewer cells as monoclonal B-cell lymphocytosis which is not recognized as either a leukemia or lymphoma. Effectively, thousands of patients in the United States alone would be re-classified as no longer having leukemia or lymphoma following the change in definitions. Dissemination of this knowledge among clinicians has been slow, however and it is unknown how this is handled in cancer registries. This only matters, of course, for lymphoma algorithms that include chronic lymphocytic leukemia/small lymphocytic lymphoma.

Because of the inconsistencies of terminology and diagnostic techniques, all future algorithms and validations in the topic of "lymphoma" need to very carefully consider and report all definitions of "lymphoma" studied, and algorithm validations should ideally include more than one cancer registry as gold standard.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

There are many different types of lymphoma and they can be separated into categories on several different properties, most of which do not track well with the ICD coding methodology. In particular, they can be separated for etiologic purposes into T-cell and B-cell lymphomas, for outcome purposes into curable and non-curable lymphomas, or for purposes of tracking intensity of therapy into aggressive or non-aggressive lymphomas. The historical approach of separating into Hodgkin or non-Hodgkin lymphoma is perhaps not as globally useful as it once was. For purposes of pharmacoepidemiologic

studies which provided the impetus for this Mini-Sentinel report, it is logical to cast a wide net of lymphoproliferative diseases and include lymphoid leukemias and perhaps even plasma cell disorders as they are more biologically related to "lymphomas" than their naming convention might suggest. The one validation study that was conducted excluded plasma cell diseases but found two basic algorithms with reasonable performance characteristics, though a higher PPV would be desirable.[1] The combination of these algorithms led to what the authors felt was the best algorithm (algorithm 3). Despite a PPV of only 56.6%, sensitivity was 88.3%, which was notably better than either algorithm alone. The first algorithm included a combination of diagnosis codes with codes for various procedures or drugs, typically on the same day. Alternatively, two diagnosis codes could occur within 12 months of one another after a diagnostic procedure with biopsy. The second algorithm required two or more lymphoma diagnosis codes within two months. The requirement of only one diagnosis code led to an unacceptable PPV. Thus, it is recommended that a single diagnosis code alone not be used to identify lymphoma. Finally, this study was limited in that it used only registry-identified cases as true positives, so the performance characteristics reported are dependent on the ability of the registry to identify all cases. This has been brought into question, particularly for less common cancers. The PPVs of the algorithms would be higher if cases not confirmed by the registry were confirmed by medical record review.

It is notable that this validation study[1] included an analysis to determine the impact of the algorithm performance characteristics on rate ratio estimates in a hypothetical cohort study examining lymphoma as an outcome of drug exposure. Rate ratios were reduced by 0.151 to 0.223, depending on the estimated prevalence of the outcome. A higher prevalence of the outcome in the study population led to greater bias in the rate ratio estimate.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

Given that only one validation study of lymphoma was identified, it focused on an older population in one state, and it considered only registry identified cases as true positives, opportunities for studying the validity of administrative data-based lymphoma definitions are many. Future research might include examining the validity of algorithms in multiple geographic settings, inclusion of plasma cell diseases, and among a broader range of ages. It is also recommended that a hybrid design be considered for future validation studies. This would involve accepting registry-confirmed cases as true positives, and conducting medical record reviews for those algorithm-identified cases that were not confirmed by the registry. This design could be more efficient than a study that requires medical record review of all cases to be validated, though it would be dependent upon linkage of the administrative data source to a cancer registry.

VII. REFERENCES

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VIII. APPENDICES

A. APPENDIX A: ABSTRACTS OF STUDIES INCLUDED IN EVIDENCE TABLES (TABLES 3 & 4)

Setoguchi S, Solomon DH, Glynn RJ, Cook EF, Levin R, Schneeweiss S. Agreement of diagnosis and its date for hematologic malignancies and solid tumors between Medicare claims and cancer registry data. *Cancer Causes & Control: CCC*. 2007; 18(5): 561-569.

Abstract: PURPOSE: Claims data may be a suitable source studying associations between drugs and cancer. However, linkage between cancer registry and claims data including pharmacy-dispensing information is not always available. We examined the accuracy of claims-based definitions of incident cancers and their date of diagnosis. METHODS: Four claims-based definitions were developed to identify incident leukemia, lymphoma, lung, colorectal, stomach, and breast cancer. We identified a cohort of subjects aged >or=65 (1997-2000) from Pennsylvania Medicare and drug benefit program data linked with the state cancer registry. We calculated sensitivity, specificity, and positive predictive values of the claims-based definitions using registry as the gold standard. We further assessed the agreement between diagnosis dates from two data sources. RESULTS: All definitions had very high specificity (>or=98%), while sensitivity varied between 40% and 90%. Test characteristics did not vary systematically by age groups. The date of first diagnosis according to Medicare data tended to be later than the date recorded in the registry data except for breast cancer. The differences in dates of first diagnosis were within 14 days for 75% to 88% of the cases. Bias due to outcome misclassification of our claims-based definition of cancer was minimal in our example of a cohort study. CONCLUSIONS: Claims data can identify incident hematologic malignancies and solid tumors with very high specificity with sufficient agreement in the date of first diagnosis. The impact of bias due to outcome misclassification and thus the usefulness of claims-based cancer definitions as cancer outcome markers in etiologic studies need to be assessed for each study setting.

Bernstein CN, Nabalamba A. Hospitalization-based major comorbidity of inflammatory bowel disease in Canada. *Canadian Journal of Gastroenterology (Journal Canadien de Gastroenterologie)*. 2007; 21(8): 507-511.

Abstract: OBJECTIVE: To define the patterns of hospitalization for known major comorbidities associated with inflammatory bowel disease (IBD) in Canada. METHODS: The data source was the Statistics Canada Health Person Oriented Information hospital database (1994/1995 to 2003/2004). The number of stays for a diagnosis of Crohn's disease or ulcerative colitis by the International Classification of Diseases, ninth edition, codes 555 or 556, or the International Classification of Diseases, 10th edition, Canadian Enhancement, codes K50 or K51, was extracted. Age- and sex-specific and age-adjusted rates of hospitalization for selected IBD-related comorbidities were assessed. RESULTS: Rates of Hodgkin's disease and non-Hodgkin's lymphoma were low in the hospitalized IBD population. Rates for colon cancer, rectal cancer, pulmonary emboli and deep venous thromboembolism were generally higher among IBD patients younger than 50 years of age compared with the non-IBD hospitalized population. CONCLUSIONS: IBD was associated with life-threatening comorbidities such as venous thromboembolic disease and colon cancer among persons younger than 50 years of age to a greater extent than the general hospitalized population. Recent secular trends in rates of non-Hodgkin's lymphomas will need to be followed to determine whether the whole population, including IBD patients who receive immunomodulating therapies, are at increased risk.

Caillard S, Agodoa LY, Bohen EM, Abbott KC. Myeloma, Hodgkin disease, and lymphoid leukemia after renal transplantation: characteristics, risk factors and prognosis. *Transplantation*. 2006; 81(6): 888-895.

Abstract: BACKGROUND: Hodgkin disease and myeloma were recently included in the classification of posttransplant lymphoproliferative disorder (PTLD). However, because their incidence is low, not much is known about their particular features. METHODS: The incidence, characteristics, risk, and prognostic factors of myeloma, Hodgkin disease, and lymphoid leukemia using the United States Renal Data System from 1991 to 2000 among 66,159 Medicare patients were analyzed. RESULTS: In all, 1,169 recipients developed a lymphoid disease: 823 (1.2%) non-Hodgkin's lymphomas (NHL), 160 (0.24%) myelomas, 60 (0.1%) Hodgkin lymphomas, and 126 (0.2%) lymphoid leukemias. Older age was associated with an increased risk of myeloma and leukemia. The incidence of hepatitis C virus infection was higher in recipients with myeloma (6.9 vs 3.9%, P=0.05). Induction therapy was associated with a greater risk of myeloma and leukemia, but not Hodgkin disease. Azathioprine was associated with a lower risk of myeloma, and tacrolimus with a lower risk of Hodgkin disease. According to the type of malignancy, ten-year survival rates were significantly different: 42, 26, 55 and 39% respectively for NHL, myeloma, Hodgkin disease, and leukemia. CONCLUSION: These results support specific features and risk factors related to the occurrence of each type of lymphoid-proliferation and suggest for the first time a possible association between hepatitis C virus and myeloma in kidney transplant recipients.

Dalager NA, Kang HK, Burt VL, Weatherbee L. Non-Hodgkin's lymphoma among Vietnam veterans. *Journal of Occupational Medicine: Official Publication of the Industrial Medical Association*. 1991; 33(7): 774-779.

Abstract: In light of findings suggesting an increase in the risk for non-Hodgkin's lymphoma among men exposed to phenoxyherbicides and concerns among veterans over Agent Orange exposure, a hospital-based case-control study was undertaken to examine the association between military service in Vietnam and non-Hodgkin's lymphoma. The cases consisted of 201 Vietnam-era veteran patients who were treated in one of 172 Department of Veterans Affairs hospitals from 1969 through 1985 with a diagnosis of non-Hodgkin's lymphoma. 358 Vietnam-era veteran patients with a diagnosis other than malignant lymphoma served as a comparison group. Military service information was obtained from a review of the veteran's military personnel records. Service in Vietnam did not increase the risk of non-Hodgkin's lymphoma either in general (branch adjusted odds ratio = 1.03, 95% confidence interval = 0.70-1.50) or with increased latency period as defined as the duration in years from first service in Vietnam to hospital discharge. Surrogate measures of potential Agent Orange exposure such as service in a specific military branch, in a certain region within Vietnam, or in a combat role as determined by military occupational speciality were not associated with any increased risk of non-Hodgkin's lymphoma.

Dalager NA, Kang HK, Burt VL, Weatherbee L. Hodgkin's disease and Vietnam service. *Ann Epidemiol*. 1995; 5(5): 400-406.

Abstract: Earlier studies that showed an association between exposure to phenoxy herbicides and the risk of malignant lymphomas have sparked concerns among Vietnam veterans over Agent Orange exposure. The Department of Veterans Affairs (VA) undertook a hospital-based case-control study to examine the association between military service in Vietnam and several histologic types of malignant lymphomas. This is a report of 283 Vietnam-era veteran patients who were treated in one of 172 VA hospitals from 1969 to 1985 with a diagnosis of Hodgkin's disease (HD). Four hundred and four Vietnam-era veteran patients with diagnosis other than malignant lymphoma served as a comparison group. Military service in Vietnam was not associated with any significant increase in

the risk of HD (adjusted odds ratio = 1.28; 95% confidence interval = 0.94, 1.76). Surrogate measures of potential Agent Orange exposure such as service in a specific military branch, in a certain region within Vietnam, in a combat role, or extended Vietnam service time were not associated with any significant increased risk of HD.

Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2004; 4(6): 905-913.

Abstract: Previous reports of cancer after kidney transplantation have been limited by small numbers of patients in single-center studies and incomplete ascertainment of cases in large registries. We examined rates of malignancies among first-time recipients of deceased or living donor kidney transplantations in 1995-2001 (n = 35 765) using Medicare billing claims. For most common tumors, e.g. colon, lung, prostate, stomach, esophagus, pancreas, ovary and breast, cancer rates were roughly twofold higher after kidney transplantation compared with the general population. Melanoma, leukemia, hepatobiliary tumors, cervical and vulvovaginal tumors were each approximately fivefold more common. Testicular and bladder cancers were increased approximately threefold, while kidney cancer was approximately 15-fold more common. Kaposi's sarcoma, non-Hodgkin's lymphomas, and nonmelanoma skin cancers were more than 20-fold increased than in the general population. Compared with patients on the waiting list, several tumors were more common after transplantation ($p < 0.01$): nonmelanoma skin cancers (2.6-fold), melanoma (2.2-fold), Kaposi's sarcoma (9.0-fold), non-Hodgkin's lymphoma (3.3-fold), cancer of the mouth (2.2-fold), and cancer of the kidney (39% higher). The rates for most malignancies are higher after kidney transplantation compared with the general population. Cancer should continue to be a major focus of prevention in kidney transplantation.

McGinnis KA, Fultz SL, Skanderson M, Conigliaro J, Bryant K, Justice AC. Hepatocellular carcinoma and non-Hodgkin's lymphoma: the roles of HIV, hepatitis C infection, and alcohol abuse. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2006; 24(31): 5005-5009.

Abstract: PURPOSE: To explore the relationship of HIV, hepatitis C (HCV), and alcohol abuse/dependence to risk for hepatocellular carcinoma and non-Hodgkin's lymphoma (NHL). PATIENTS AND METHODS: Male veterans (n = 14,018) with a first HIV diagnosis in the Veterans Affairs Healthcare System from October 1997 to September 2004; and 28,036 age-, race-, sex-, and location-matched HIV-negative veterans were identified. We examined the incidence of hepatocellular carcinoma and NHL and presence of HCV and alcohol abuse/dependence using International Classification of Diseases, ninth revision (ICD-9-CM) codes. HIV-positive to HIV-negative incident rate ratios (IRRs) and 95% CIs for the occurrence of hepatocellular carcinoma and NHL were calculated using Poisson regression models. RESULTS: HIV-positive veterans were at greater risk for hepatocellular carcinoma than HIV-negative veterans (IRR = 1.68; 95% CI, 1.02 to 2.77). After adjusting for HCV infection and alcohol abuse/dependence, HIV status was not independently associated with hepatocellular cancer (IRR = 0.96; 95% CI, 0.56 to 1.63). HIV-positive veterans had 9.71 times (95% CI, 6.99 to 13.49) greater risk of NHL than HIV-negative veterans. After adjusting for HCV and alcohol abuse/dependence, the IRR for NHL comparing HIV-positive with HIV-negative veterans is similar (IRR = 10.03, 95% CI, 7.19 to 13.97). CONCLUSION: HIV-positive veterans have a higher relative incidence of hepatocellular carcinoma and NHL than HIV-negative veterans. For hepatocellular carcinoma, this association appears to be largely explained by the higher prevalence of HCV and alcohol abuse/dependence. Efforts to decrease hepatocellular carcinoma

among persons with HIV should focus primarily on detecting and treating HCV and reducing heavy alcohol use.

Namboodiri KK, Harris RE. Hematopoietic and lymphoproliferative cancer among male veterans using the Veterans Administration Medical System. *Cancer*. 1991; 68(5): 1123-1130.

Abstract: Hematopoietic and lymphoproliferative cancer risk among the 3.7 million United States male veterans who use the Veterans Administration (VA) medical system annually was assessed using age-specific incidence curves and cumulative incidence rates. Relative risk comparing the VA with general population risk estimates from the Surveillance, Epidemiology, and End Results (SEER) data were increased significantly for all malignancies examined. The VA sample showed risk increases of 93% for Hodgkin's disease, 20% for non-Hodgkin's lymphomas, 51% for multiple myelomas, and 40% for all leukemias. Among the leukemia subtypes, the observed risk increases were 54%, 23%, 80%, and 46% for lymphocytic, granulocytic, monocytic, and other forms of leukemia, respectively. The large size of the sample and the consistency of risk estimates with two different methods confer validity and strength to these findings. The possible relevance of the high prevalence of tobacco and alcohol use in this population sample to the current findings is discussed and the need for further analytic investigations to explain the increases in risk is emphasized.

Shea AM, Curtis LH, Hammill BG, DiMartino LD, Abernethy AP, Schulman KA. Association between the Medicare Modernization Act of 2003 and patient wait times and travel distance for chemotherapy. *JAMA*. 2008; 300(2): 189-196.

Abstract: CONTEXT: The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) altered reimbursements for outpatient chemotherapy drugs and drug administration services. Anecdotal reports suggest that these adjustments may have negatively affected access to chemotherapy for Medicare beneficiaries. OBJECTIVE: To compare patient wait times and travel distances for chemotherapy before and after the enactment of the MMA. DESIGN, SETTING, AND PATIENTS: Analysis of a nationally representative 5% sample of claims from the Centers for Medicare & Medicaid Services for the period 2003 through 2006. Patients were Medicare beneficiaries with incident breast cancer, colorectal cancer, leukemia, lung cancer, or lymphoma who received chemotherapy in inpatient hospital, institutional outpatient, or physician office settings. MAIN OUTCOME MEASURES: Days from incident diagnosis to first chemotherapy visit and distance traveled for treatment, controlling for age, sex, race/ethnicity, cancer type, geographic region, comorbid conditions, and year of diagnosis and treatment. RESULTS: There were 5082 incident cases of breast cancer, colorectal cancer, leukemia, lung cancer, or lymphoma in 2003; 5379 cases in 2004; 5116 cases in 2005; and 5288 cases in 2006. Approximately 70% of patients received treatment in physician office settings in each year. Although the distribution of treatment settings in 2004 and 2005 was not significantly different from 2003 (P = .24 and P = .72, respectively), there was a small but significant change from 2003 to 2006 (P = .02). The proportion of patients receiving chemotherapy in inpatient settings decreased from 10.2% in 2003 to 8.8% in 2006 (P = .03), and the proportion in institutional outpatient settings increased from 21.1% to 22.5% (P = .004). The proportion in physician offices remained at 68.7% (P = .29). The median time from diagnosis to initial chemotherapy visit was 28 days in 2003, 27 days in 2004, 29 days in 2005, and 28 days in 2006. In multivariate analyses, average wait times for chemotherapy were 1.96 days longer in 2005 than in 2003 (95% confidence interval [CI], 0.11-3.80 days; P = .04) but not significantly different in 2006 (0.88 days; 95% CI, -0.96 to 2.71 days; P = .35). Median travel distance was 7 miles (11.2 km) in 2003 and 8 miles (12.8 km) in 2004 through 2006. After adjustment, average travel distance remained slightly longer in 2004 (1.47 miles [2.35 km]; 95% CI, 0.87-2.07 miles [1.39-3.31 km]; P < .001), 2005

(1.19 miles [1.90 km]; 95% CI, 0.58-1.80 miles [0.93-2.88 km]; P < .001), and 2006 (1.30 miles [2.08 km]; 95% CI, 0.69-1.90 miles [1.10-3.04 km]; P < .001) compared with 2003. CONCLUSION: There have not been major changes in travel distance and patient wait times for chemotherapy in the Medicare population since 2003, the year before MMA-related changes in reimbursement.

Smith JM, Rudser K, Gillen D, Kestenbaum B, Seliger S, Weiss N, et al. Risk of lymphoma after renal transplantation varies with time: an analysis of the United States Renal Data System. *Transplantation*. 2006; 81(2): 175-180.

Abstract: BACKGROUND: Characterization of the incidence of posttransplant lymphoma over time may help guide the timing and intensity of posttransplant monitoring. We analyzed the United States Renal Data System to describe the occurrence of lymphoma following renal transplantation. METHODS: All end-stage renal disease patients placed on the transplant waiting list between January 1, 1990 and December 31, 1999 were considered. Survival analysis was used to estimate lymphoma risk in renal transplant patients. RESULTS: Of 89,260 eligible patients, a total of 556 lymphoma cases were identified with 357 in transplant patients. The overall rate of posttransplant lymphoma was 33.3/10,000 person-years in transplant patients. There was variation in the duration and magnitude of increased lymphoma risk by age. The highest rates of lymphoma were among transplanted patients in the first 12 months, after which the rate of lymphoma decreased. Among Caucasian transplant recipients less than 25 years of age, the adjusted relative risk of lymphoma ranged from 13.82 [95% CI: (3.96, 48.15)] within 6 months posttransplant to 3.46 [95% CI: (0.69, 17.44)] within months 30-36 posttransplant. Only patients under 25 years had a notably increased risk beyond the first 2 posttransplant years. The risk of lymphoma differed by race, with Caucasian patients at nearly double the risk of African-Americans. Gender was not associated with lymphoma incidence. CONCLUSIONS: We found and quantified a time-varying relationship between renal transplant and lymphoma risk. This information can be used in combination with knowledge of established risk factors to guide the schedule of posttransplant monitoring.

Watanabe KK, Kang HK, Thomas TL. Mortality among Vietnam veterans: with methodological considerations. *Journal of Occupational Medicine: Official Publication of the Industrial Medical Association*. 1991; 33(7): 780-785.

Abstract: The Department of Veterans Affairs previously conducted a proportionate mortality study of Army and Marine Vietnam-era veterans who died during 1965 through 1982. In the present study, 11,325 veterans who died during 1982 through 1984 and 50,743 veterans from the previous analysis made up the final sample of 62,068 veterans. When compared with all non-Vietnam veterans, Army Vietnam veterans had statistically significant excesses of deaths from external causes (proportionate mortality ratio [PMR] = 1.03), laryngeal cancer (PMR = 1.53), and lung cancer (PMR = 1.08). Marine Vietnam veterans had a significantly elevated PMR for external causes (PMR = 1.06) with a significant excess of homicide deaths (PMR = 1.16) when compared to all non-Vietnam veterans. The elevated PMRs for lung cancer and non-Hodgkin's lymphoma among Marine Vietnam veterans reported in the earlier VA study persisted when compared with Marine non-Vietnam veterans. However, it was found that these elevations probably were due to a deficit among the Marine non-Vietnam veterans rather than an excess among Marine Vietnam veterans.

B. APPENDIX B: LIST OF CITATIONS SELECTED FOR FULL-TEXT REVIEW BUT NOT INCLUDED, BY REASONS FOR EXCLUSION

1. Studies Excluded Due to Poorly Defined Algorithms

Al-Mansour M, Connors JM, Gascoyne RD, Skinnider B, Savage KJ. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2010; 28(5): 793-9.

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Au WY, Gascoyne RD, Gallagher RE, Le N, Klasa RD, Liang RHS, et al. Hodgkin's lymphoma in Chinese migrants to British Columbia: a 25-year survey. *Annals of Oncology: Official Journal of the European Society for Medical Oncology / ESMO*. 2004; 15(4): 626-30.

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C. APPENDIX C: LIST AND DEFINITIONS OF ICD OR PROCEDURAL CODES INCLUDED IN ALGORITHMS

Table C1. Codes for Cancers

Description	ICD-8-CM	ICD-9-CM	ICD-10-CM
Soft tissue sarcoma		171.x	
Kaposi's sarcoma		176.x	
Lymphomas	200.x-202.x	200.x- 202.x	
Non-Hodgkin's lymphoma (Lymphosarcoma)	200.x	200.x	C83.x, C85.x
Small lymphocytic lymphoma		200.0	C83.0
Malignant lymphoma, Diffuse		200.1	C83.2
Burkitt lymphoma		200.2	C83.7
Marginal zone lymphoma		200.3	
Mantle cell lymphoma		200.4	
Lymphoplasmacytic lymphoma		200.6	
Diffuse large B cell lymphoma		200.7	C85.1
Non-Hodgkin's lymphosarcoma NOS		200.8, 200.9	C83.8, C83.9
Hodgkin's lymphoma	201.	201.	C81.x
Non-Hodgkin's lymphoma (Lymphoid/histiocytic)	202.x	202.x	C82.x, C84.x
Malignant lymphoma, Follicular		202.0	C82.x
Mycosis Fungoides/Sezary disease		202.1, 202.2	C84.0, C84.1
Percutaneous & Peripheral T cell lymphomas		202.7	C84.2
Peripheral T-cell lymphomas		202.7	C84.4
NK/other T-cell lymphomas		202.8, 202.9	C84.5
NHL Lymphoid/histiocytic NOS			C85.7, C85.9
Myeloma		203.x	C90.x
Lymphoid leukemia		204.x	C91.x
Lymphoblastic leukemia (Acute lymphocytic leukemia)		204.0	C91.0
Chronic lymphocytic leukemia		204.1	C91.1
Leukemia		205.x-208.x	C92.x-C95.x

Table C2. Codes for Cancer-Related Complications, Procedures, or Treatments, from Setoguchi, et al.[1]

Type of Code	Definition	Code(s)
ICD-9	Hypercalcemia	275.4x
ICD-9	Secondary malignant neoplasm of brain and spinal cord	198.3
ICD-9	Unspecified disease of the spinal cord	336.9
ICD-9	Superior vena cava syndrome	459.2
CPT	Pain management or palliative care	99551, 99552
CPT	Diagnostic procedures with biopsy	38500, 38505, 38510, 38520, 38525, 38530, 38542, 49180, 76003, 76360, 76365, 76942, 88170, 88171, 88172, 88173, 85095, 85097, 85102, 38220, 38221, 38100, 38101, 38102, 38115, 38589, 38562, 38564, 38570, 61332, 54550, 54505, 54512, 54520, 54530, 19100, 19101, 19102, 42826, 11100, 11101
CPT	Cancer chemotherapies	36640, 51720, 96400, 96405, 96406, 96408, 96410, 96412, 96414, 96420, 96422, 96423, 96425, 96440, 96445, 96450, 96500, 96501, 96504, 96505, 96508, 96510, 96511, 96512, 96520, 96524, 96530, 96538, 96540, 96542, 96545, 96549, 96450, 99555
CPT	Cancer-related radiations	77261, 77262, 77263, 77280, 77285, 77290, 77295, 77299, 77300, 77305, 77310, 77315, 77321, 77326, 77327, 77328, 77331, 77332, 77333, 77334, 77336, 77370, 77399, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77417, 77419, 77420, 77425, 77430, 77431, 77432, 77470, 77499, 76960, 55859, 55860, 55862, 55865, 77750, 77761, 77762, 77763, 77776, 77777, 77778, 77781, 77782, 77783, 77784, 77789, 77790, 77799, 79200, 79300, 79400, 79420, 79440, 79900, 79999
CPT	Hematopoietic transplantations	38230, 38231, 38240, 38241, 38242

Table C3. New Codes as of 2007 within the 200.x, 201.x, 202.x, or 204.x Ranges

In 2007, a substantial change in ICD-9 coding for lymphoma resulted in the adoption of 54 new lymphoma codes. The following table details current lymphoma codes based on that revision.[17,18]

ICD-9 Code 5 digits	Definition
200.00	Reticulosarcoma, unspecified site
200.01	Reticulosarcoma involving lymph nodes of head, face, and neck
200.02	Reticulosarcoma involving intrathoracic lymph nodes
200.03	Reticulosarcoma involving intra-abdominal lymph nodes
200.04	Reticulosarcoma involving lymph nodes of axilla and upper limb
200.05	Reticulosarcoma involving lymph nodes of inguinal region and lower limb
200.06	Reticulosarcoma involving intrapelvic lymph nodes
200.07	Reticulosarcoma involving spleen
200.08	Reticulosarcoma involving lymph nodes of multiple sites
200.10	Lymphosarcoma, unspecified site
200.11	Lymphosarcoma involving lymph nodes of head, face, and neck
200.12	Lymphosarcoma involving intrathoracic lymph nodes
200.13	Lymphosarcoma involving intra-abdominal lymph nodes
200.14	Lymphosarcoma involving lymph nodes of axilla and upper limb
200.15	Lymphosarcoma involving lymph nodes of inguinal region and lower limb
200.16	Lymphosarcoma involving intrapelvic lymph nodes
200.17	Lymphosarcoma involving spleen
200.18	Lymphosarcoma involving lymph nodes of multiple sites
200.20	Burkitt's tumor or lymphoma, unspecified site
200.21	Burkitt's tumor or lymphoma involving lymph nodes of head, face, and neck
200.22	Burkitt's tumor or lymphoma involving intrathoracic lymph nodes
200.23	Burkitt's tumor or lymphoma involving intra-abdominal lymph nodes
200.24	Burkitt's tumor or lymphoma involving lymph nodes of axilla and upper limb
200.25	Burkitt's tumor or lymphoma involving lymph nodes of inguinal region and lower limb
200.26	Burkitt's tumor or lymphoma involving intrapelvic lymph nodes
200.27	Burkitt's tumor or lymphoma involving spleen
200.28	Burkitt's tumor or lymphoma involving lymph nodes of multiple sites
200.30	Marginal zone lymphoma, unspecified site, extranodal and solid organ sites
200.31	Marginal zone lymphoma, lymph nodes of head, face, and neck

200.32	Marginal zone lymphoma, intrathoracic lymph nodes
200.33	Marginal zone lymphoma, intraabdominal lymph nodes
200.34	Marginal zone lymphoma, lymph nodes of axilla and upper limb
200.35	Marginal zone lymphoma, lymph nodes of inguinal region and lower limb
200.36	Marginal zone lymphoma, intrapelvic lymph nodes
200.37	Marginal zone lymphoma, spleen
200.38	Marginal zone lymphoma, lymph nodes of multiple sites
200.40	Mantle cell lymphoma, unspecified site, extranodal and solid organ sites
200.41	Mantle cell lymphoma, lymph nodes of head, face, and neck
200.42	Mantle cell lymphoma, intrathoracic lymph nodes
200.43	Mantle cell lymphoma, intra-abdominal lymph nodes
200.44	Mantle cell lymphoma, lymph nodes of axilla and upper limb
200.45	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
200.46	Mantle cell lymphoma, intrapelvic lymph nodes
200.47	Mantle cell lymphoma, spleen
200.48	Mantle cell lymphoma, lymph nodes of multiple sites
200.50	Primary central nervous system lymphoma, unspecified site, extranodal and solid organ sites
200.51	Primary central nervous system lymphoma, lymph nodes of head, face, and neck
200.52	Primary central nervous system lymphoma, intrathoracic lymph nodes
200.53	Primary central nervous system lymphoma, intra-abdominal lymph nodes
200.54	Primary central nervous system lymphoma, lymph nodes of axilla and upper limb
200.55	Primary central nervous system lymphoma, lymph nodes of inguinal region and lower limb
200.56	Primary central nervous system lymphoma, intrapelvic lymph nodes
200.57	Primary central nervous system lymphoma, spleen
200.58	Primary central nervous system lymphoma, lymph nodes of multiple sites
200.60	Anaplastic large cell lymphoma, unspecified site, extranodal and solid organ sites
200.61	Anaplastic large cell lymphoma, lymph nodes of head, face, and neck
200.62	Anaplastic large cell lymphoma, intrathoracic lymph nodes
200.63	Anaplastic large cell lymphoma, intra-abdominal lymph nodes
200.64	Anaplastic large cell lymphoma, lymph nodes of axilla and upper limb
200.65	Anaplastic large cell lymphoma, lymph nodes of inguinal region and lower limb
200.66	Anaplastic large cell lymphoma, intrapelvic lymph nodes
200.67	Anaplastic large cell lymphoma, spleen
200.68	Anaplastic large cell lymphoma, lymph nodes of multiple sites

200.70	Large cell lymphoma, unspecified site, extranodal and solid organ sites
200.71	Large cell lymphoma, lymph nodes of head, face, and neck
200.72	Large cell lymphoma, intrathoracic lymph nodes
200.73	Large cell lymphoma, intra-abdominal lymph nodes
200.74	Large cell lymphoma, lymph nodes of axilla and upper limb
200.75	Large cell lymphoma, lymph nodes of inguinal region and lower limb
200.76	Large cell lymphoma, intrapelvic lymph nodes
200.77	Large cell lymphoma, spleen
200.78	Large cell lymphoma, lymph nodes of multiple sites
200.80	Other named variants of lymphosarcoma and reticulosarcoma, unspecified site
200.81	Other named variants of lymphosarcoma and reticulosarcoma involving lymph nodes of head, face, and neck
200.82	Other named variants of lymphosarcoma and reticulosarcoma involving intrathoracic lymph nodes
200.83	Other named variants of lymphosarcoma and reticulosarcoma involving intra-abdomnial lymph nodes
200.84	Other named variants of lymphosarcoma and reticulosarcoma involving lymph nodes of axilla and upper limb
200.85	Other named variants of lymphosarcoma and reticulosarcoma involving lymph nodes of inguinal region and lower limb
200.86	Other named variants of lymphosarcoma and reticulosarcoma involving intrapelvic lymph nodes
200.87	Other named variants of lymphosarcoma and reticulosarcoma involving spleen
200.88	Other named variants of lymphosarcoma and reticulosarcoma involving lymph nodes of multiple sites
201.00	Hodgkin's paragranuloma, unspecified site
201.01	Hodgkin's paragranuloma involving lymph nodes of head, face, and neck
201.02	Hodgkin's paragranuloma involving intrathoracic lymph nodes
201.03	Hodgkin's paragranuloma involving intra-abdominal lymph nodes
201.04	Hodgkin's paragranuloma involving lymph nodes of axilla and upper limb
201.05	Hodgkin's paragranuloma involving lymph nodes of inguinal region and lower limb
201.06	Hodgkin's paragranuloma involving intrapelvic lymph nodes
201.07	Hodgkin's paragranuloma involving spleen
201.08	Hodgkin's paragranuloma involving lymph nodes of multiple sites
201.10	Hodgkin's granuloma, unspecified site
201.11	Hodgkin's granuloma involving lymph nodes of head, face, and neck
201.12	Hodgkin's granuloma involving intrathoracic lymph nodes
201.13	Hodgkin's granuloma involving intra-abdominal lymph nodes
201.14	Hodgkin's granuloma involving lymph nodes of axilla and upper limb

201.15	Hodgkin's granuloma involving lymph nodes of inguinal region and lower limb
201.16	Hodgkin's granuloma involving intrapelvic lymph nodes
201.17	Hodgkin's granuloma involving spleen
201.18	Hodgkin's granuloma involving lymph nodes of multiple sites
201.20	Hodgkin's sarcoma, unspecified site
201.21	Hodgkin's sarcoma involving lymph nodes of head, face, and neck
201.22	Hodgkin's sarcoma involving intrathoracic lymph nodes
201.23	Hodgkin's sarcoma involving intra-abdominal lymph nodes
201.24	Hodgkin's sarcoma involving lymph nodes of axilla and upper limb
201.25	Hodgkin's sarcoma involving lymph nodes of inguinal region and lower limb
201.26	Hodgkin's sarcoma involving intrapelvic lymph nodes
201.27	Hodgkin's sarcoma involving spleen
201.28	Hodgkin's sarcoma involving lymph nodes of multiple sites
201.40	Hodgkin's disease, lymphocytic-histiocytic predominance, unspecified site
201.41	Hodgkin's disease, lymphocytic-histiocytic predominance involving lymph nodes of head, face, and neck
201.42	Hodgkin's disease, lymphocytic-histiocytic predominance involving intrathoracic lymph nodes
201.43	Hodgkin's disease, lymphocytic-histiocytic predominance involving intra- abdominal lymph nodes
201.44	Hodgkin's disease, lymphocytic-histiocytic predominance involving lymph nodes of axilla and upper limb
201.45	Hodgkin's disease, lymphocytic-histiocytic predominance involving lymph nodes of inguinal region and lower limb
201.46	Hodgkin's disease, lymphocytic-histiocytic predominance involving intrapelvic lymph nodes
201.47	Hodgkin's disease, lymphocytic-histiocytic predominance involving spleen
201.48	Hodgkin's disease, lymphocytic-histiocytic predominance involving lymph nodes of multiple sites
201.50	Hodgkin's disease, nodular sclerosis, unspecified site
201.51	Hodgkin's disease, nodular sclerosis, involving lymph nodes of head, face, and neck
201.52	Hodgkin's disease, nodular sclerosis, involving intrathoracic lymph nodes
201.53	Hodgkin's disease, nodular sclerosis, involving intra-abdominal lymph nodes
201.54	Hodgkin's disease, nodular sclerosis, involving lymph nodes of axilla and upper limb
201.55	Hodgkin's disease, nodular sclerosis, involving lymph nodes of inguinal region and lower limb
201.56	Hodgkin's disease, nodular sclerosis, involving intrapelvic lymph nodes
201.57	Hodgkin's disease, nodular sclerosis, involving spleen
201.58	Hodgkin's disease, nodular sclerosis, involving lymph nodes of multiple sites
201.60	Hodgkin's disease, mixed cellularity, unspecified site
201.61	Hodgkin's disease, mixed cellularity, involving lymph nodes of head, face, and neck

201.62	Hodgkin's disease, mixed cellularity, involving intrathoracic lymph nodes
201.63	Hodgkin's disease, mixed cellularity, involving intra-abdominal lymph nodes
201.64	Hodgkin's disease, mixed cellularity, involving lymph nodes of axilla and upper limb
201.65	Hodgkin's disease, mixed cellularity, involving lymph nodes of inguinal region and lower limb
201.66	Hodgkin's disease, mixed cellularity, involving intrapelvic lymph nodes
201.67	Hodgkin's disease, mixed cellularity, involving spleen
201.68	Hodgkin's disease, mixed cellularity, involving lymph nodes of multiple sites
201.70	Hodgkin's disease, lymphocytic depletion, unspecified site
201.71	Hodgkin's disease, lymphocytic depletion, involving lymph nodes of head, face, and neck
201.72	Hodgkin's disease, lymphocytic depletion, involving intrathoracic lymph nodes
201.73	Hodgkin's disease, lymphocytic depletion, involving intra-abdominal lymph nodes
201.74	Hodgkin's disease, lymphocytic depletion, involving lymph nodes of axilla and upper limb
201.75	Hodgkin's disease, lymphocytic depletion, involving lymph nodes of inguinal region and lower limb
201.76	Hodgkin's disease, lymphocytic depletion, involving intrapelvic lymph nodes
201.77	Hodgkin's disease, lymphocytic depletion, involving spleen
201.78	Hodgkin's disease, lymphocytic depletion, involving lymph nodes of multiple sites
201.90	Hodgkin's disease, unspecified type, unspecified site
201.91	Hodgkin's disease, unspecified type, involving lymph nodes of head, face, and neck
201.92	Hodgkin's disease, unspecified type, involving intrathoracic lymph nodes
201.93	Hodgkin's disease, unspecified type, involving intra-abdominal lymph nodes
201.94	Hodgkin's disease, unspecified type, involving lymph nodes of axilla and upper limb
201.95	Hodgkin's disease, unspecified type, involving lymph nodes of inguinal region and lower limb
201.96	Hodgkin's disease, unspecified type, involving intrapelvic lymph nodes
201.97	Hodgkin's disease, unspecified type, involving spleen
201.98	Hodgkin's disease, unspecified type, involving lymph nodes of multiple sites
202.00	Nodular lymphoma, unspecified site
202.01	Nodular lymphoma involving lymph nodes of head, face, and neck
202.02	Nodular lymphoma involving intrathoracic lymph nodes
202.03	Nodular lymphoma involving intra-abdominal lymph nodes
202.04	Nodular lymphoma involving lymph nodes of axilla and upper limb
202.05	Nodular lymphoma involving lymph nodes of inguinal region and lower limb
202.06	Nodular lymphoma involving intrapelvic lymph nodes
202.07	Nodular lymphoma involving spleen
202.08	Nodular lymphoma involving lymph nodes of multiple sites

202.10	Mycosis fungoides, unspecified site
202.11	Mycosis fungoides involving lymph nodes of head, face, and neck
202.12	Mycosis fungoides involving intrathoracic lymph nodes
202.13	Mycosis fungoides involving intra-abdominal lymph nodes
202.14	Mycosis fungoides involving lymph nodes of axilla and upper limb
202.15	Mycosis fungoides involving lymph nodes of inguinal region and lower limb
202.16	Mycosis fungoides involving intrapelvic lymph nodes
202.17	Mycosis fungoides involving spleen
202.18	Mycosis fungoides involving lymph nodes of multiple sites
202.20	Sezary's disease, unspecified site
202.21	Sezary's disease involving lymph nodes of head, face, and neck
202.22	Sezary's disease involving intrathoracic lymph nodes
202.23	Sezary's disease involving intra-abdominal lymph nodes
202.24	Sezary's disease involving lymph nodes of axilla and upper limb
202.25	Sezary's disease involving lymph nodes of inguinal region and lower limb
202.26	Sezary's disease involving intrapelvic lymph nodes
202.27	Sezary's disease involving spleen
202.28	Sezary's disease involving lymph nodes of multiple sites
202.30	Malignant histiocytosis, unspecified site
202.31	Malignant histiocytosis involving lymph nodes of head, face, and neck
202.32	Malignant histiocytosis involving intrathoracic lymph nodes
202.33	Malignant histiocytosis involving intra-abdominal lymph nodes
202.34	Malignant histiocytosis involving lymph nodes of axilla and upper limb
202.35	Malignant histiocytosis involving lymph nodes of inguinal region and lower limb
202.36	Malignant histiocytosis involving intrapelvic lymph nodes
202.37	Malignant histiocytosis involving spleen
202.38	Malignant histiocytosis involving lymph nodes of multiple sites
202.40	Leukemic reticuloendotheliosis, unspecified site
202.41	Leukemic reticuloendotheliosis involving lymph nodes of head, face, and neck
202.42	Leukemic reticuloendotheliosis involving intrathoracic lymph nodes
202.43	Leukemic reticuloendotheliosis involving intra-abdominal lymph nodes
202.44	Leukemic reticuloendotheliosis involving lymph nodes of axilla and upper arm
202.45	Leukemic reticuloendotheliosis involving lymph nodes of inguinal region and lower limb
202.46	Leukemic reticuloendotheliosis involving intrapelvic lymph nodes

202.47	Leukemic reticuloendotheliosis involving spleen
202.48	Leukemic reticuloendotheliosis involving lymph nodes of multiple sites
202.50	Letterer-siwe disease, unspecified site
202.51	Letterer-siwe disease involving lymph nodes of head, face, and neck
202.52	Letterer-siwe disease involving intrathoracic lymph nodes
202.53	Letterer-siwe disease involving intra-abdominal lymph nodes
202.54	Letterer-siwe disease involving lymph nodes of axilla and upper limb
202.55	Letterer-siwe disease involving lymph nodes of inguinal region and lower limb
202.56	Letterer-siwe disease involving intrapelvic lymph nodes
202.57	Letterer-siwe disease involving spleen
202.58	Letterer-siwe disease involving lymph nodes of multiple sites
202.60	Malignant mast cell tumors, unspecified site
202.61	Malignant mast cell tumors involving lymph nodes of head, face, and neck
202.62	Malignant mast cell tumors involving intrathoracic lymph nodes
202.63	Malignant mast cell tumors involving intra-abdominal lymph nodes
202.64	Malignant mast cell tumors involving lymph nodes of axilla and upper limb
202.65	Malignant mast cell tumors involving lymph nodes of inguinal region and lower limb
202.66	Malignant mast cell tumors involving intrapelvic lymph nodes
202.67	Malignant mast cell tumors involving spleen
202.68	Malignant mast cell tumors involving lymph nodes of multiple sites
202.70	Peripheral T cell lymphoma, unspecified site, extranodal and solid organ sites
202.71	Peripheral T cell lymphoma, lymph nodes of head, face, and neck
202.72	Peripheral T cell lymphoma, intrathoracic lymph nodes
202.73	Peripheral T cell lymphoma, intra-abdominal lymph nodes
202.74	Peripheral T cell lymphoma, lymph nodes of axilla and upper limb
202.75	Peripheral T cell lymphoma, lymph nodes of inguinal region and lower limb
202.76	Peripheral T cell lymphoma, intrapelvic lymph nodes
202.77	Peripheral T cell lymphoma, spleen
202.78	Peripheral T cell lymphoma, lymph nodes of multiple sites
202.80	Other malignant lymphomas, unspecified site
202.81	Other malignant lymphomas involving lymph nodes of head, face, and neck
202.82	Other malignant lymphomas involving intrathoracic lymph nodes
202.83	Other malignant lymphomas involving intra-abdominal lymph nodes
202.84	Other malignant lymphomas involving lymph nodes of axilla and upper limb

202.85	Other malignant lymphomas involving lymph nodes of inguinal region and lower limb
202.86	Other malignant lymphomas involving intrapelvic lymph nodes
202.87	Other malignant lymphomas involving spleen
202.88	Other malignant lymphomas involving lymph nodes of multiple sites
202.90	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue, unspecified site
202.91	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue involving lymph nodes of head, face, and neck
202.92	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue involving intrathoracic lymph nodes
202.93	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue involving intra-abdominal lymph nodes
202.94	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue involving lymph nodes of axilla and upper limb
202.95	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue involving lymph nodes of inguinal region and lower limb
202.96	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue involving intrapelvic lymph nodes
202.97	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue involving spleen
202.98	Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue involving lymph nodes of multiple sites
204.00	Lymphoid leukemia, acute, without mention of remission
204.01	Lymphoid leukemia, acute, in remission
204.10	Lymphoid leukemia, chronic, without mention of remission
204.11	Lymphoid leukemia, chronic, in remission
204.20	Lymphoid leukemia, subacute, without mention of remission
204.21	Lymphoid leukemia, subacute, in remission
204.80	Other lymphoid leukemia, without mention of remission
204.81	Other lymphoid leukemia, in remission
204.90	Unspecified lymphoid leukemia, without mention of remission
204.91	Unspecified lymphoid leukemia, in remission