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

PULMONARY FIBROSIS, INTERSTITIAL LUNG DISEASE REPORT

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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

Pulmonary Fibrosis, Interstitial Lung Disease Report

I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT

The 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 pulmonary fibrosis (PF) algorithm review.

B. SUMMARY OF FINDINGS

Of the searched and reviewed studies, there were 5 identified that used coding algorithms for pulmonary fibrosis (PF) or interstitial lung disease (ILD). There were no validation studies identified among the reviewed studies.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

There were only 5 studies that provided codes for PF or ILD. The codes primarily used for PF included: International Classification of Disease, Ninth Revision (ICD-9) code 515 (chronic postinflammatory fibrosis) and 516.3 (idiopathic fibrosing alveolitis). One of the studies used ICD-10 code J84.1 (other interstitial pulmonary diseases with fibrosis, including fibrosing alveolitis [cryptogenic], Hamman-Rich syndrome, and idiopathic pulmonary fibrosis) to specifically identify idiopathic PF cases. Another study used ICD-9 codes 516.8 and 516.9 (other/unspecified alveolar pneumonopathies, respectively) in addition to ICD-9 code 515 (chronic postinflammatory fibrosis) and 516.3 (idiopathic fibrosing alveolitis) to identify ILD cases. Procedural codes were used as well to narrow the definition of ILD. None of these 5 studies provided any validation procedures or validation estimates.

II. PROJECT OBJECTIVES

The primary objective of this project was to identify studies that used validated algorithms 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 5 validation studies were identified, a secondary objective was to identify non-validated algorithms that were used to identify the HOIs using administrative data.

III. BACKGROUND

The 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 (HOIs) 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 HOIs, based on several criteria. These criteria included: 1) previous validation studies that were identified in a textbook chapter reviewing the validity of drug and diagnosis data used in pharmacoepidemiologic studies,[1] 2) a list of designated medical events from a proposed FDA rule on the safety reporting requirements for human drug and biological products,[2] and 3) the Observational Medical Outcomes Partnership (OMOP)'s[i] commissioned reports on algorithms used to identify health outcomes using administrative data.[3]

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

Pulmonary fibrosis (PF) was one of the 20 HOIs selected for review. This report describes the review process and findings for the PF 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 2 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 1 set of OMOP reports (angioedema)[4, 5] 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 2 sets of files, 1 containing the abstracts for review and the other for documenting abstract-review results.

The search strategy and results for pulmonary fibrosis are detailed in the Results section. The PubMed and IDIS searches were conducted on June 22, 2010.

[i] For more information, visit the OMOP website.

B. ABSTRACT REVIEW

1. Abstract Review Methods

Each abstract was reviewed independently by 2 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 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, as validation components of studies are not necessarily included in the abstract and other relevant citations might be identified from the references of such studies.

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 2 investigators, with the 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, because 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 2 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 decision.

2. Full-text Exclusion Criteria

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 to diagnostic methods currently used in clinical practice. This included whether certain diagnostic 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 is included in the Results section.

V. RESULTS

A. SEARCH STRATEGY AND RESULTS

The following summarizes the search results obtained from PubMed and IDIS searches. The PubMed search identified 203 citations (Table 1), and the IDIS search identified 7 unique citations (Table 2). The total number of unique citations from the combined searches was 210.

Table 1. PubMed Search Strategy and Results (203): Performed on 06/22/10

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	1863249
#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	373384

	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 "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	109612
#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	2603134
#5	Search #3 NOT #4 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	69912
#6	("interstitial"[All Fields] and ("lung"[All Fields] OR "pulmonary"[All Fields])) OR "Lung Diseases, Interstitial"[Mesh] OR ("Pulmonary Fibrosis"[Mesh] OR ("pulmonary"[All Fields] AND "fibrosis"[All Fields]) OR "pulmonary fibrosis"[All Fields] OR "idiopathic pulmonary fibrosis"[MeSH Terms] OR ("idiopathic"[All Fields] AND "pulmonary"[All Fields] AND "fibrosis"[All Fields]) OR "idiopathic pulmonary fibrosis"[All Fields]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	26103
#7	Search #5 AND #6 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	203

Table 2. IDIS Search Strategy and Results (7 unique citations): Performed on 06/22/10

Disease(s):

"FIBROSIS, PULMONARY 515." or "DISEASE, LUNG NEC 518."

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") and ("SIDE EF RESPIRATORY 79")

AND Abstract:

("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")

Years: 1990-2010

B. ABSTRACT REVIEWS

Of the 210 abstracts reviewed, 20 were selected for full-text review. Because of the straightforward inclusion criteria, consisting of: 1) examination of the HOI of interest, 2) use of administrative database, and 3) study conducted in the United States or Canada, the 2 reviewers achieved perfect agreement on acceptance/rejection status. Agreement on the reason of rejection was also generally high; among the 190 rejected abstracts, inter-rater agreement (via Cohen's kappa coefficient) was 0.70, 0.69, and 0.81 for the 3 inclusion criteria, respectively. As only a single rejection reason was captured in our abstract review database, this overwhelming consensus illustrates that the classification process was generally not complicated.

C. FULL-TEXT REVIEWS

Perfect agreement between reviewers was also achieved during full-text review of the 20 articles selected via abstract review. Reviewers concurred that none of these 20 articles included validation of the outcome definition or reported validity estimates. Because no validation studies were identified, 5 studies that did not include validation of the outcome or report validity statistics but fulfilled all other criteria were reviewed and incorporated into the evidence table.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators provided no published or unpublished reports of validation studies that were completed by their teams. They also did not provide any published reports that they were familiar with but not directly involved in.

E. EVIDENCE INCLUDED IN TABLE

Because no validation studies were identified, 5 studies that did not include validation of the outcome or report validity statistics were reviewed and incorporated in the evidence table. 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. We only came across 5 studies that provided codes for PF or interstitial lung disease (ILD). Suissa, et al.[6] used ICD-9 codes 515, 516.3, 516.8, and 516.9 to identify spontaneous reports of ILD among patients with rheumatoid arthritis. Raghu, et al.[7] used ICD-9 code 516.3 as the basis of their broad and narrow idiopathic pulmonary fibrosis (IPF) definitions. Ehrlich, et al.[8] used ICD-9 codes 515 and 516.3 to identify PF in patients with and without diabetes. Pinheiro, et al.[9] used the ICD-10 code J84.1 to identify occupational risks for IPF. Finally, ICD-9 code 501 and ICD-10 code J61 were used by Gan, et al.[10] to identify asbestosis, a special type of PF/ILD occurring from asbestos exposure. The definitions of these codes as well as the specific disease(s) each code was used to identify are presented in Table 1.

The most elaborate algorithm was used by Raghu, et al.,[7] and as such deserves additional explanation. They developed both broad and narrow case definitions for IPF. Their broad definition used ICD-9 code 516.3 and incorporated an exclusion criterion defined as a medical encounter with a diagnosis code for any other type of ILD. Their narrow definition of IPF expanded on this broad definition by incorporating procedural codes for surgical lung biopsy (ICD-9-CM 33.28, 34.21; Current Procedural Terminology, Fourth Edition [CPT-4] 32095, 32100–32160, 32602), transbronchial lung biopsy (ICD-9-CM 33.27; CPT-4 31628, 31629), and computed tomography of the thorax (ICD-9-CM 87.41; CPT-4 71250, 71260, 71270).[7]

Validation Algorithms. None of these 5 studies provided any validation procedures or validation statistics. Because we did not come across any other studies that provided any codes for this HOI, we included only 5 studies in the table.

Several ICD-9 codes were used to identify cases with PF/ILD. Additional procedural codes were applied to narrow case identification. None of these studies validated their case-identification algorithms. To enhance generalizability of findings in those studies, it is merited to validate these coding algorithms in different population groups and health care settings.

Selected Patient Populations. The studies also varied with respect to patient population. Beyond the demographic differences described below, clinical differences were evident.

Ehrlich, et al.[8] examined PF as well as pulmonary conditions (asthma, chronic obstructive pulmonary disease [COPD], pneumonia, and lung cancer) in patients with a diagnosis of diabetes (and a non-diabetic comparison group). Gan, et al.[10] focused on surveillance of asbestosis. Pinheiro, et al.[9] examined

occupational risks for IPF mortality, while Raghu, et al.[7] focused on all-cause IPF. Suissa, et al.[6] studied the risk of ILD in patients with rheumatoid arthritis treated with leflunomide.

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

As indicated in section F above, there was variation in the demographic characteristics between the 5 studies with PF algorithms (but without validation statistics). Two of these studies used state-specific or regional data. Ehrlich, et al.[8] used data from the Kaiser Permanente Medical Care program in Northern California on patients <18 years as of January 1, 1996. Gan, et al.[10] used data, predominantly from males (1121 men, 49 women), from the British Columbia Linked Health Database; new asbestosis cases between 1992 and 2004 were identified using workers' compensation records (n=271), hospitalization records (n=562), and outpatient records (n=582).

The 3 remaining studies used data of a more national breadth. Pinheiro, et al.[9] used data from the US National Institute for Occupational Safety and Health (NIOSH) mortality surveillance system for respiratory diseases of occupational interest; US residents who were 15 years or older between 1999 and 2003 were studied. Raghu, et al.[7] used data from an unspecified health care claims processing system of a large US health plan that consisted of claims for service facilities (e.g., hospitals), health care professionals (e.g., physicians), and retail pharmacies and provided services through health maintenance organizations, preferred provider organizations, Medicare Risk, and indemnity products to approximately 3 million persons residing in 20 states. Subjects were 18 years or older and were eligible for comprehensive health benefits for at least 1 day during calendar year 2000. Last, Suissa, et al.[6] used data from September 1, 1998–December 31, 2003 from the PharMetrics Patient-Centric Database; subjects were 18 years of age or older at cohort entry.

H. EVIDENCE TABLE

Table 3. Non-validated Algorithms

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm
Ehrlich, et al. 2010 [8]	Kaiser Permanente Medical Care program in Northern California. The study cohort (n=121,886) was drawn from a population of 1,811,228 members aged <18 years as of 1 January 1996.	Incidence of asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, and lung cancer in patients with and without a diagnosis of diabetes.	Pulmonary fibrosis, ICD-9 515 (chronic postinflammatory) and 516.3 (idiopathic).
Gan, et al. 2009 [10]	British Columbia Linked Health Database (BCLHD) data, individuals ≥15 years of age. The study cohort included 1170 new asbestosis cases (1121 men, 49 women) identified using workers' compensation records (n=271), hospitalization records (n=562), and outpatient records (n=582) from 1992–2004.	Population-based surveillance of asbestosis using multiple health data sources.	ICD-9 code 501 (asbestosis) and ICD-10 code J61 (pneumoconiosis due to asbestos and other mineral fibers), to identify asbestosis cases.
Pinheiro, et al. 2008[9]	United States National Institute for Occupational Safety and Health (NIOSH) mortality surveillance system for respiratory diseases of occupational interest; multiple cause-of-death data compiled by the National Center for Health Statistics for US residents aged 15 years and older, 1999–2003.	Idiopathic pulmonary fibrosis mortality rate and occupational risks.	The term "IPF" refers here to the group of diseases classified under ICD-10 code J84.1, comprising "Other interstitial pulmonary diseases with fibrosis, including fibrosing alveolitis (cryptogenic), Hamman-Rich syndrome, and idiopathic pulmonary fibrosis." Cases were defined as those decedents whose death certificates mentioned ICD-I0 code J84.1 (i.e., IPF) as the underlying or contributing cause of death and did not mention any other type or cause of interstitial lung disease.
Raghu, et al. 2006[7]	Unspecified data source. Data were obtained from the health care claims processing system of a large US health plan (1996–2000) that consisted of claims for service facilities (e.g., hospitals), health care professionals (e.g., physicians), and retail pharmacies and provided services through health maintenance	Annual incidence and prevalence of Idiopathic pulmonary fibrosis in the United States.	Algorithms with "broad" and "narrow" case definitions of IPF. Persons with IPF were identified on the basis of the following: (1) 1 or more medical encounters with a diagnosis code for IPF (ICD-9-CM 516.3) between January 1, 1996 (or their date of health-plan enrollment, whichever was later) and December 31, 2000 (or their date of health-plan disenrollment, whichever occurred first) and (2) no medical encounters with a diagnosis code for any

	organizations, preferred provider organizations, Medicare Risk, and indemnity products to approximately 3 million persons residing in 20 states. The study sample consisted of all persons 18 years or older who were eligible for comprehensive health benefits for at least 1 day in calendar year (CY) 2000.		other type of ILD on or after the date of their last medical encounter with a diagnosis of IPF ("broad case definition"). Because a diagnosis of IPF is more likely to be accurate if based on appropriate testing, the authors also used an alternative ("narrow") case definition in which they required that persons with IPF (1) satisfy the broad case definition set forth above and (2) have 1 or more medical encounters with a procedure code for surgical lung biopsy (ICD-9-CM 33.28, 34.21; CPT-4 32095, 32100–32160, 32602), transbronchial lung biopsy (ICD-9-CM 33.27; CPT-4 31628, 31629), or computed tomography of the thorax (ICD-9-CM 87.41; CPT-4 71250, 71260, 71270) on or before the date of their last medical encounter with a diagnosis of IPF. Persons whose first medical encounter with a diagnosis code for IPF was in CY2000 and who were continuously eligible for health benefits for at least 365 days before the date of that encounter, including those with and without surgical lung biopsy, transbronchial lung biopsy, and computed tomography of the thorax, also were identified. All such persons were designated as having "newly diagnosed" (i.e., incident) disease.
Suissa, et al. 2006 [6]	PharMetrics Patient-Centric Database, September 1, 1998–December 31, 2003. Subjects were 18 years of age or older at cohort entry.	Risk of ILD in patients with rheumatoid arthritis treated with leflunomide.	Cases of probable drug-related ILD were identified from inpatient encounters as all subjects who were hospitalized with a first-time primary diagnosis of postinflammatory lung fibrosis (ICD-9 code 515), idiopathic fibrosing alveolitis (code 516.3), or other/unspecified alveolar pneumonopathies (codes 516.8 and 516.9). As a sensitivity analysis, the authors expanded the case definition to include ILD identified from outpatient encounters as well as a mention of the relevant codes as secondary diagnoses during inpatient encounters. Respiratory disease codes that might signal the presence of ILD prior to cohort entry were defined as any diagnosis of postinflammatory lung fibrosis (ICD-9 code 515), idiopathic fibrosing alveolitis (516.3), and other or unspecified alveolar pneumonopathies (516.8 and 516.9) appearing on any outpatient claim or as a secondary diagnosis on inpatient claims during the year prior to cohort entry.

I. CLINICIAN OR TOPIC-EXPERT CONSULTATION

ILDs are a diverse group of pulmonary disorders classified together because of similar clinical, physiologic, or pathologic features.[11] Therefore, as it pertains to this current review, the operational definition of PF/ILD is broad and needs further specification. In medical literature and clinical practice, PF is considered a subtype of ILD. In terms of epidemiology, the incidence of ILD is approximately 30 per 100,000; about half of these cases are classified as PF.[11] The diversity of the diseases classified under ILD is well illustrated in Raghu, et al.,[7] who identified 35 ICD-9 codes, used as exclusion criteria in their IPF definition, falling within the ILD definition.

We found that ILD was defined via 4 ICD-9-CM codes, specifically 515, 516.3, 516.8, and 516.9. Only the ICD-9-CM codes 515 and 516.3 were used to define PF. IPF, a subtype of PF, was defined only by ICD-9-CM code 516.3. Indeed, the use of diagnostic codes in the literature reviewed appears to coincide with the scope of the definition in clinical practice.

There are, however, potential concerns rooted in the broadness or narrowness of the ICD-9-CM definitions. For instance, ICD-9-CM codes 515 and 516.3 were used to identify both ILD and PF, but without the broader-defined ICD-9-CM codes of 516.8 and 516.9, other forms of ILD would be missed. However, these broader codes incorporate rare conditions such as lipoid pneumonia and therefore may be too extensive to identify PF and, to a lesser extent, ILD. Similarly, the ICD-9-CM code 516.3 was used to identify IPF, a subtype of PF; however, this code includes other rare conditions such as Hamman-Rich syndrome.

Fine tuning of PF/ILD algorithms may be possible via application of additional criteria such as relevant procedural codes; such strategies have been applied to narrow case identification.[7] These procedural codes may help to differentiate PF/ILD from other conditions affecting lungs and the respiratory system overall. For example, Raghu, et al.[7] narrowed their IPF algorithm by requiring cases to have 1 or more medical encounters with a procedure code for surgical lung biopsy, transbronchial lung biopsy, or computed tomography of the thorax. These procedural codes certainly added specificity to the algorithm, and in fact reduced the number of IPF patients identified by approximately 3-fold.[7] There are, however, limiting factors that must be considered when using these or any procedural codes. Mainly, when the tests are being done for differential diagnostic purposes, administrative claims data do not generally include information on the results of these procedures and do not specify whether the diagnosis was confirmed. Also, procedures often may not have been carried out on chronic patients within the study index period, especially if patients received their diagnosis outside the study period. Therefore, including these procedural codes in the algorithm may exclude those patients with PF/ILD and reduce the sensitivity of the algorithm.

Algorithm development may be further hindered because both PF and ILD are rare conditions. Depending on the type and specialization of health care providers and settings of health care, the choice of the diagnostic codes may vary. For example, we speculate that the codes chosen may be associated with the perceived certainty in the diagnosis, which may vary between specialists and primary care providers. Likewise, there may be differences in inpatient and outpatient settings. These all can potentially result in variations of diagnostic codes being captured in automated health care databases and may potentially influence algorithm development.

It is worth noting here that on October 1, 2013, medical coding in US health care settings will change from ICD-9 to ICD-10. The transition will result in business and systems changes throughout the health

care industry, including health plans and health care practice and research. All HIPAA transactions, including outpatient claims with dates of service and inpatient claims with dates of discharge, will use ICD-10 codes starting in October 2013. The ICD-10 section and the subcodes for J84 (other interstitial pulmonary diseases) are related to PF/ILD.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

There are almost certainly definitional problems pertaining to each of the existing codes used to identify PF and ILD. However, the extent of these problems cannot be known, as there are no validation studies. We suspect that ICD-9-CM codes 515 and 516.3 are most likely too narrow to identify all PF/ILD cases. By contrast, the ICD-9-CM codes 516.8 and 516.9 have more extensive definitions and are perhaps used when there is uncertainty about a specific PF/ILD diagnosis. Therefore, using these codes for case identification, even in combination with procedural codes, may not provide the desired levels of sensitivity and specificity.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

Due to the scarcity of literature providing validated or non-validated algorithms for PF/ILD, we suggest that research needs to be conducted on designing validation studies to test PF/ILD algorithms and estimating their predictive power, sensitivity, and specificity.

VII. REFERENCES

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6. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis Rheum*. May 2006; 54(5): 1435-1439.

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VIII. APPENDICES

A. APPENDIX A: ABSTRACTS OF STUDIES INCLUDED IN EVIDENCE TABLE

Ehrlich SF, Quesenberry CP Jr, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care*. 2010; 33(1): 55–60.

OBJECTIVE: There are limited data on the risk of pulmonary disease in patients with diabetes. The aim of this study was to evaluate and compare the incidence of asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, and lung cancer in patients with and without a diagnosis of diabetes. RESEARCH DESIGN AND METHODS: We conducted a retrospective, longitudinal cohort study using the electronic records of a large health plan in northern California. Age and sex data were available for all cohort members (n = 1,811,228). Data on confounders were available for a subcohort that responded to surveys (n = 121,886), among whom Cox proportional hazards regression models were fit. RESULTS: Age- and sex-adjusted incidence rates and 95% CIs were calculated for members with and without diabetes in the full cohort and the subcohort. No difference was observed for lung cancer, but the incidence of asthma, COPD, fibrosis, and pneumonia was significantly higher in those members with a diagnosis of diabetes. These differences remained significant in regression models adjusted for age, sex, race/ethnicity, smoking, BMI, education, alcohol consumption, and outpatient visits (asthma hazard ratio [HR] 1.08 [95% CI 1.03-1.12], COPD HR 1.22 [1.15-1.28], pulmonary fibrosis HR 1.54 [1.31-1.81], and pneumonia HR 1.92 [1.84-1.99]). The risk of pneumonia and COPD increased significantly with increasing A1C. CONCLUSIONS: Individuals with diabetes are at increased risk of several pulmonary conditions (asthma, COPD, fibrosis, and pneumonia) but not lung cancer. This increased risk may be a consequence of declining lung function in patients with diabetes.

Gan WQ, Demers PA, McLeod CB, Koehoorn M. Population-based asbestosis surveillance in British Columbia. *Occupational and Environmental Medicine*. 2009; 66(11): 766–771.

OBJECTIVES: To investigate the use of multiple health data sources for population-based asbestosis surveillance in British Columbia, Canada. METHODS: Provincial health insurance registration records, workers' compensation records, hospitalisation records, and outpatient medical service records were linked using individual-specific study identifiers. The study population was restricted to individuals > or = 15 years of age living in the province during 1992-2004. RESULTS: 1170 new asbestosis cases were identified from 1992 to 2004 for an overall incidence rate of 2.82 (men: 5.48, women: 0.23) per 100,000 population; 96% of cases were male and average (SD) age was 69 (10) years. Although the annual number of new cases increased by 30% during the surveillance period (beta = 2.36, p = 0.019), the observed increase in annual incidence rates was not significant (beta = 0.02, p = 0.398). Workers' compensation, hospitalisation and outpatient databases identified 23%, 48% and 50% of the total new cases, respectively. Of the new cases, 82% were identified through single data sources, 10% were only recorded in the workers' compensation records, and 36% only in each of the hospitalisation and outpatient records. 84% of hospitalisation cases and 83% of outpatient cases were not included in the workers' compensation records. The three data sources showed different temporal trends in the annual number of new cases and annual incidence rates. CONCLUSIONS: Single data sources were not sufficient to identify all new cases, thus leading to serious underestimations of the true burden of asbestosis. Integrating multiple health data sources could provide a more complete picture in population-based surveillance of asbestosis and other occupational diseases.

Pinheiro GA, Antao VC, Wood JM, Wassell JT. Occupational risks for idiopathic pulmonary fibrosis mortality in the United States. *International Journal of Occupational and Environmental Health*. 2008; 14(2): 117–123.

Metal and wood dust exposures have been identified as possible occupational risk factors for idiopathic pulmonary fibrosis (IPF). We analyzed mortality data using ICD-10 code J84.1--"Other interstitial pulmonary diseases with fibrosis," derived age-adjusted mortality rates for 1999-2003, and assessed occupational risks for 1999, by calculating proportionate mortality ratios (PMRs) and mortality odds ratios (MORs) using a matched case-control approach. We identified 84,010 IPF deaths, with an age-adjusted mortality rate of 75.7 deaths/million. Mortality rates were highest among males, whites, and those aged 85 and older. Three industry categories with potential occupational exposures recognized as risk factors for IPF were identified: "Wood buildings and mobile homes" (PMR = 4.5, 95% confidence interval (CI) 1.2-11.6 and MOR = 5.3, 95% CI 1.2-23.8), "Metal mining" (PMR = 2.4, 95% CI 1.3-4.0 and MOR = 2.2, 95% CI 1.1-4.4), and "Fabricated structural metal products" (PMR = 1.9, 95% CI 1.1-3.1 and MOR = 1.7, 95% CI 1.0-3.1). Workers in these industry categories may benefit from toxicological studies and improved surveillance for this disease.

Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine*. 2006; 174(7): 810–816.

RATIONALE: Idiopathic pulmonary fibrosis is a chronic interstitial lung disease of unknown etiology; its epidemiology in the United States has not been well characterized. OBJECTIVE: To estimate the annual incidence and prevalence of idiopathic pulmonary fibrosis in the United States. METHODS: Retrospective cohort design utilizing a large health care claims database spanning the period January 1996 through December 2000. MEASUREMENTS AND MAIN RESULTS: Persons with idiopathic pulmonary fibrosis were identified based on diagnosis and procedure codes. Using broad case-finding criteria, prevalence was estimated to range from 4.0 per 100,000 persons aged 18 to 34 yr to 227.2 per 100,000 among those 75 yr or older; annual incidence was estimated to range from 1.2 to 76.4 per 100,000. Using narrow case-finding criteria, prevalence ranged from 0.8 to 64.7 per 100,000 persons; comparable figures for incidence were 0.4 to 27.1 per 100,000 persons. Extrapolating these rates to the overall United States' population, prevalence was estimated to be 42.7 per 100,000 (incidence, 16.3 per 100,000) using broad criteria; with narrow criteria, prevalence was estimated to be 14.0 per 100,000 (incidence, 6.8 per 100,000). CONCLUSIONS: Our results suggest that idiopathic pulmonary fibrosis is probably more common in the United States than previously reported.

Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. *Arthritis and Rheumatism*. 2006; 54(5): 1435–1439.

OBJECTIVE: Spontaneous reports of interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) treated with leflunomide, a disease-modifying antirheumatic drug (DMARD), have been appearing recently. To assess this risk, we conducted a population-based epidemiologic study. METHODS: A cohort of 62,734 patients with RA to whom a DMARD had been dispensed between September 1, 1998 and December 31, 2003 was formed using the PharMetrics claims database. A nested case-control design was used, in which each case of serious ILD requiring hospitalization was matched to 100 controls according to age (calendar time) and equal or greater duration of followup, to estimate adjusted rate ratios (RRs) of serious ILD associated with DMARD use. RESULTS: There were 74 cases of serious ILD, which corresponds to a rate of 8.1 per 10,000 patients per year. The risk of ILD was increased with the use of leflunomide (adjusted RR 1.9 [95% confidence interval (95%

CI) 1.1-3.6]). Among subjects with no previous methotrexate use and no history of ILD, the risk associated with leflunomide treatment was not elevated (RR 1.2 [95% CI 0.4-3.1]), but it was elevated among the remaining subjects (RR 2.6 [95% CI 1.2-5.6]). Patients with a history of ILD were twice as likely to have been prescribed leflunomide as any other DMARD. CONCLUSION: The reports of ILD associated with leflunomide use are likely the result of channeling of high-risk patients to leflunomide treatment, particularly those with a history of methotrexate use or preexisting ILD. Patients with no history of ILD and no previous methotrexate use show no excess risk of developing ILD with leflunomide treatment.

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

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2. Studies Excluded Due to a Lack of Validation or Reporting of Validation Statistics

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3. Other Excluded Studies

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

Type of Code (e.g., ICD-9, ICD-10, CPT)	Code	Description	Disease(s) Defined
ICD-9	515	Pulmonary fibrosis (chronic postinflammatory)	PF, ILD
ICD-9	516.3	Idiopathic fibrosing alveolitis	PF, IPF, ILD
ICD-9	516.8 and 516.9	Other/unspecified alveolar pneumonopathies	ILD
ICD-10	J84.1	Other interstitial pulmonary diseases with fibrosis, including fibrosing alveolitis (cryptogenic), Hamman-Rich syndrome, and idiopathic pulmonary fibrosis	IPF
ICD-9	501	Asbestosis	Asbestosis
ICD-10	J61	Pneumoconiosis due to asbestos and other mineral fibers	Asbestosis