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

PANCREATITIS REPORT

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

Pancreatitis 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 pancreatitis algorithm review.

B. SUMMARY OF FINDINGS

A total of 9 validation studies were found for inclusion in this report. The studies reported on the presence of diagnostic codes for pancreatitis in either hospital based or ambulatory based medical records or billing databases, although hospital records were predominant. Studies reported both incident and prevalent outcomes. The algorithm could be present as the primary discharge diagnosis, or it could be present in any position, or it was not specified. The most frequent positive predictive values were in the range of 60-80%, however some were as low as 20% and others were as high as 97%, depending on the algorithm used and the methods of validation. The algorithms were highly sensitive (>90%) in those studies that performed random sampling of eligible subjects without the diagnostic code present in their record, and these studies included populations at increased risk compared to the general population. The populations in the studies included some that were at high risk of pancreatitis such as heavy alcohol users, HIV infected patients, and dialysis patients. There were also populations that were representative of the level of pancreatitis risk of the US population in general, though only one of the two included multiple hospitals. The age range of subjects included pediatric patients as well as the general age of the most common occurrences of pancreatitis, which is in the mid-forties to mid-fifties. There were relatively few subjects that were of an age greater than 70 years. Some studies involved patients in whom the etiology of pancreatitis was primarily related to alcohol use but overall the populations were typical for etiologies related to: gallstones, alcohol, endoscopic retrograde cholangiopancreatography (ERCP), hyperlipidemia, drugs, malignancy, and idiopathic. The geographic distribution of the populations was reasonably complete with studies representing Arkansas, Ohio, Kentucky, California, Connecticut, Pennsylvania, and Michigan. The time period of data collection in these studies cover a range from the early 1980's up to 2007.

C. RECOMMENDATION FOR ALGORITHMS AND SUGGESTION FOR FUTURE RESEARCH

The most common algorithm used was for acute pancreatitis and was based on the ICD-9 code 577.0. The PPV for this algorithm ranged from a low of 40% to a high of 97%, with the majority of data indicating a PPV of approximately 70%. The higher rates of PPV were found when it was specified that the code was in the primary position of the discharge diagnosis. The sensitivity of this algorithm is high, approximately 99% based on the limited evidence in which it was assessed. Validation of the algorithm was most often based on finding 2 of 3 of the following in the medical record: the presence of typical symptoms of pain, an elevation of serum amylase or lipase, or evidence of pancreatitis by imaging. This is consistent with the American College of Gastroenterology Guidelines and the American

Gastroenterological Association Technical Review for the diagnosis of acute pancreatitis.[6, 7] The imaging study most recommended by these organizations for confirmation of pancreatitis is computed tomography.

In some studies either ICD-9 code 577.0 acute pancreatitis or ICD-9 code 577.1 chronic pancreatitis could be present in the record to identify a case of pancreatitis. This is appropriate if the goal of the record screening is to identify either form of the disease. It may also have the potential to increase sensitivity of the algorithm, though potentially at the risk of specificity if chronic pancreatitis is not the health outcome of interest. No studies were found in which 577.1 was the only diagnostic code in the record screening. Use of ICD-9 code 577.1 may have particularly poor PPV as it can include both recurrent acute pancreatitis and chronic pancreatitis. Current definitions of recurrent acute pancreatitis and chronic pancreatitis, as well as the absence of an alternative diagnosis for abdominal pain and mild pancreatic enzyme elevations, are problematic when using administrative data for this outcome.

It may be helpful for additional studies to evaluate the performance of the single ICD-9 code 577.0 compared to permitting either code 577.0 or 577.1 to be present. One study also used CPT codes 82150 or 83690 for either serum levels of amylase or lipase, and ICD-9 codes for nausea or vomiting (787.03), abdominal pain (789.0), and abdominal tenderness (789.60-789.69). It may be helpful to determine if these codes increase sensitivity of an algorithm. However based on current evidence, use of these codes would most likely significantly decrease specificity of screening without a substantial increase in sensitivity. There are no studies which have used ICD-10 codes for pancreatitis.

Studies that included a primary hospital discharge diagnosis of ICD-9-CM code 577.0 had the best PPV and specificity. This algorithm has been evaluated in a wide range of individual populations, with some involving high risk individuals (heavy alcohol use, dialysis, HIV, gallstones) and others including typical risk populations. Some studies involved pediatric patients and other studies included the primary age range of this condition (i.e., 45 – 55 years of age). Collectively, the studies have included individuals with various etiologies for pancreatitis and have been conducted in a wide geographic distribution. The additional inclusion of 577.1 and 577.2 does not have the literature support to recommend use. Due to the variability in performance characteristics identified and single center nature of most studies, it may be useful to perform validation studies that use case finding algorithms from large administrative databases with broad population bases. Databases that are enhanced with actual laboratory data gathered at point of admission could lend additional confidence in selecting the best algorithm.

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 FDA's 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,[1] 2) a list of designated medical events had been developed 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)[i] had commissioned reports on algorithms used to identify the health outcome using administrative data.[3]

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.

Pancreatitis was one of the 20 HOIs selected for review. This report describes the review process and findings for the pancreatitis 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)[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 two sets of files, one containing the abstracts for review and the other for documenting abstract review results.

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

The search strategy and results for pancreatitis are detailed in the Results section. The PubMed and IDIS searches were both conducted 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, 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 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

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 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.

V. RESULTS

A. SEARCH STRATEGY AND RESULTS

The following tables summarize the search results obtained from PubMed and IDIS searches. The PubMed search identified 138 citations (Table 1), and the two IDIS searches identified 21 unique citations (Table 2). The total number of unique citations from the combined searches was 158.

Table 1. PubMed Search Strategy and Results (138): Performed on 06/23/10

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 "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	373522

#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	((((((((("pancreatitis"[All Fields]) OR "pancreatitis/chemically induced"[All Fields]) OR "pancreatitis/diagnosis"[All Fields]) OR "pancreatitis/epidemiology"[All Fields]) OR "pancreatitis acute necrotizing"[All Fields]) OR "pancreatitis acute"[All Fields]) OR "pancreatitis, acute"[All Fields]) OR "pancreatitis, acute necrotizing"[All Fields]) OR "pancreatitis, acute necrotizing/diagnosis"[All Fields]) OR "pancreatitis, acute necrotizing/epidemiology"[All Fields]) OR "pancreatitis, acute necrotizing/etiology"[All Fields] Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	16101
#7	("Pancreatitis"[Mesh] OR "Pancreatitis, Acute Necrotizing"[Mesh]) Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	11939
#8	#6 OR #7 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	16101
#9	Search #5 AND #8 Limits: Humans, English, Publication Date from 1990/01/01 to 2011/01/01	138

Table 2. IDIS Search Strategy and Results (21): Performed on 06/23/10

Search 1: 19 Results

ADVANCED SEARCH

Search 1:

All Fields:

pancreati* and ("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 **Descriptor(s):**

"SIDE EF DIGESTIVE 78" not ("CASE REPORT ADULT 0" or "FDA APPROVAL PACKAGE 155" OR "FDA BLACK BOX WARNING 165" OR "PIVOTAL STUDY 162" OR "FDA ADVISORY COMMITTEE 164" 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 NOT **Author(s):** "(editorial)" or "(Letter to Ed)"

Years: 1990-2010

Records = 19

Search 2: 2 Results

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):**

577.*

AND NOT **Descriptor(s):**

"CASE REPORT ADULT 0" or "FDA APPROVAL PACKAGE 155" OR "FDA BLACK BOX WARNING 165" OR "PIVOTAL STUDY 162" OR "FDA ADVISORY COMMITTEE 164" 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 NOT **Author(s):**

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

Years:

1990-2010

Records = 2

B. ABSTRACT REVIEWS

Of the 158 abstracts reviewed, 62 were selected for full-text review; 40 were excluded because they did not study pancreatitis, 42 were excluded because they were not administrative database studies, and 14 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..

C. FULL-TEXT REVIEWS

Of the 62 full-text articles reviewed, 6 were included in the final evidence tables; 23 were excluded because the HOI identification algorithm was poorly defined, and 21 were excluded because they included no validation of the outcome definition or reporting of validity statistics. Reviewers identified 2 citations for review from full-text article references. Both were included in the final report. Cohen's kappa for agreement between reviewers on inclusion vs exclusion of full-text articles reviewed was 0.77.

D. MINI-SENTINEL INVESTIGATOR SURVEY

Mini-Sentinel investigators provided no validation studies for inclusion in the report.

E. EVIDENCE INCLUDED IN TABLE

Of the 9 studies included in the table, 6 were identified from the initial search strategy, 2 were identified through references of articles that underwent full-text review, and 0 were provided by Mini-Sentinel Investigators. One additional study with a validated algorithm has been published since the time the

original search was done; that study has been added in the summary of algorithms below and in Table 3 of algorithm validation studies.

F. SUMMARY AND DISCUSSION OF ALGORITHMS AND VALIDATION

All publications listed in the evidence table used an ICD-9 code to identify patients with pancreatitis. The majority of studies used ICD-9 code 577.0 for acute pancreatitis. Some used both 577.0 and 577.1 for chronic pancreatitis. One study also used 577.2, which represents cyst and pseudocyst of the pancreas. Use of that additional code most likely produced a low specificity without increasing sensitivity for either acute or chronic pancreatitis and is not recommended. One study also used CPT codes 82150 or 83690 for either serum levels of amylase or lipase, and ICD-9 codes 787.03 for nausea or vomiting, 789.0 for abdominal pain, and 789.60-789.69 for abdominal tenderness. It may be helpful for further research to determine if these codes increase sensitivity of an algorithm. However, based on current evidence use of those codes would most likely significantly decrease specificity without a substantial increase in sensitivity.

Validation of the algorithm was primarily done by review of medical records. Validation of pancreatitis was based on physician notes on the description of the patient's pain and the presence of an elevated serum amylase or elevated lipase. In some instances the physician's note of a presumptive diagnosis of pancreatitis was sought and in some cases evidence of pancreatitis documented by imaging was considered. The most common imaging study was computed tomography. These methods for validation are consistent with the standards for the diagnosis of pancreatitis.

The various studies collectively included a broad range of subject characteristics to encompass the important ranges of age, gender, high risk and typical risk levels for pancreatitis, a full range of the most common etiologies of pancreatitis, some cases of prevalent as well as incident pancreatitis, and broad geographic distribution. Identification of the outcome was primarily based on hospital records, but some were based on outpatient electronic records or claims databases as well.

Yadav, et al., studied a population of male veterans with an average age of 47.6 years; 43.6% were white and all had heavy alcohol use. [8] The prevalence of pancreatitis (either acute or chronic) was 3 % in this population; 93% of these cases were believed to be caused by alcohol. Inclusion of the ICD-9 code for acute pancreatitis (577.0) or for chronic pancreatitis (577.1) could have been determined on the basis of either an inpatient or an outpatient evaluation. Overall chart review verified 40 of the 87 patients to have a confirmed diagnosis of pancreatitis, (PPV=46%). If both ICD-9 codes were present in the patient's record the PPV was 77%. If only the code for acute pancreatitis (577.0) was present the PPV was 40% while the PPV was 20% if the record contained only the code for chronic pancreatitis (577.1). A random sample of 214 patients without an ICD-9 code for pancreatitis, taken from the population of 1409 eligible, found a negative predictive value of 99%.

Guo, et al., studied the incidence of acute pancreatitis in a population of 4972 Ohio Medicaid patients being treated for HIV infection. [9] They used an algorithm of an ICD-9 code 577.0 and at least one lab order for either amylase or lipase indicated by CPT codes 82150 or 83690 within 30 days before or after the date of diagnosis. The ICD-9 code could be present in either inpatient or outpatient medical claims. The mean age of this population was 36.1 years (4.5% were less than 18 and 7.9% were between 50-64), 27% were female, 48% were Caucasian, 44% were African American, 10% had diabetes, 44% had a preexisting mental illness, and patients ≥65 yrs of age were excluded. The cases of pancreatitis in patients with newly treated HIV were incident cases; the incidence rate was 1.95 per 100 person-years.

The cumulative incidence of pancreatitis was 4.2% in patients who were newly treated for HIV infection and 2.6% for those whose HIV infection had been diagnosed previously. Unfortunately, although a validation procedure for the algorithm was described in the methods of this study, the results were not reported. The author was contacted to determine if this information was available, but no response was received.

McMenamin, et al., studied a population with a discharge diagnosis code for acute pancreatitis. [10] The population included 44% women, average age of 42, and a typical range of likely etiologies for acute pancreatitis with alcohol, unknown, ERCP, drug, bilestones, hyperlipidemia, and malignancy. This sample was entirely from hospitalized patients, however acute pancreatitis is most often a diagnosis made after hospital admission rather than as an outpatient. Although this is from a single center, the population characteristics are representative of the majority of individuals with acute pancreatitis from the most common causes. Medical records were available for 95 of the 115 cases and were reviewed for clinical evidence of pancreatitis. The results of the validation process demonstrated a PPV of 76.8%.

Morton, et al., studied a population of individuals who had a first hospitalization for pancreatitis in a base population of 129,000 enrolled in the Kaiser Permanente Medical Care Program in San Francisco. [11] The computerized medical records were screened for a primary discharge diagnosis code of 577.x (diseases of the pancreas). Of the 439 subjects with pancreatitis, 48.5% were < 50 years of age and 51.5% were ≥ 50 years of age, 50% were men, 51% were white or Hispanic, 35% were black, and 7.5% were Asian. The etiology of pancreatitis in this sample was consistent with the population of cases of pancreatitis as a whole, with cholelithiasis 38%, alcohol 29%, idiopathic 25%, and miscellaneous (trauma, post ERCP, cancer, HIV, hypertriglyceridemia) 8%. The total incidence rate was 0.28 per 1,000 person-years. This study did not distinguish between acute or chronic pancreatitis, though only the first hospitalization for pancreatitis was considered. In addition, mild cases of pancreatitis may not be hospitalized and may go undiagnosed. The PPV was 97%, calculated based on the proportion of potential cases excluded due to no evidence of pancreatitis in their medical records.

Park, et al., studied acute pancreatitis in children. The mean age was 13.1 (standard deviation 5.64), 40% male, 53% white, 23% black, and 19% Hispanic. [12] The most common causes of acute pancreatitis were biliary (32.6%), medications (25.6%), idiopathic (20%), systemic (10%), trauma (9%), viral infection (8%),metabolic condition (5%), and ERCP (4%). This population was hospitalized at a tertiary referral center. The algorithm for acute pancreatitis was presumably an ICD-9 code of 577.0. A total of 282 patients were identified by ICD-9 codes; 215 met the inclusion criteria of a confirmed case of pancreatitis, while 18 were excluded as chronic pancreatitis. The others had incomplete data. Although not reported by the authors, 215 confirmed cases of pancreatitis in the sample of 282 represents a PPV of 76.2%. However, if the 18 with chronic pancreatitis are also considered confirmed the PPV is 82.6%. It cannot be determined how many of the subjects with incomplete data in fact had acute pancreatitis; if they did, this would increase the PPV even more.

Quraishi, et al., studied patients in the Henry Ford Health System (HFHS) in Detroit who were initiated on dialysis after January 1, 1998. [13] Data were collected retrospectively from January 1, 1998 to August 1, 2003. They used an algorithm of ICD-9 codes for pancreatitis and pancreatitis-related complications in the admitting and discharge diagnoses. The following ICD-9 codes were used: 577.0, 577.1, and 577.2. There were a total of 128 patients identified by at least one of these ICD-9 codes. Electronic medical records and paper charts were reviewed for evidence of acute pancreatitis defined by the presence of abdominal pain in association with elevation of serum amylase and/or lipase more than three times the

upper limit of normal and the absence of any other clinical syndrome that could produce a similar clinical presentation. No information about abdominal symptoms or elevated enzyme levels were found for 80 patients, 14 had cholecystitis with no evidence of acute pancreatitis, and 6 had diabetic ketoacidosis with no evidence of acute pancreatitis. Only 28 met the criteria for acute pancreatitis, for a PPV of 22%). A total of 107 patients without ICD-9 codes for pancreatitis, but with elevated amylase or lipase, were found in electronic records. Manual chart review found that none of these patients met criteria for acute pancreatitis. The authors did not report specific performance statistics of the algorithm. It is unclear whether multiple ICD-9 codes, in particular 577.2, were included in order to produce high sensitivity at the expense of specificity of the algorithm. That appears to be true, but the authors did not address this issue or report which ICD-9 codes were most commonly reported.

Dore, et al., estimated the positive predictive value of claims for acute pancreatitis among initiators of antihyperglycemic drugs between June 1, 2005 and December 31, 2007, in the Normative Health Information (NHI) database. [14] The NHI dataset is a commercial health insurance transaction database that records ICD-9 and CPT codes. Among 260,255 initiators of antihyperglycemic drugs, medical records were sought for 842 potential cases of acute pancreatitis with an ICD-9 code of 577.0 in any position of an emergency department or hospitalization claim. Two practicing gastroenterologists assessed each case of the 585 charts that were obtained to confirm the diagnosis of acute pancreatitis based on the presence of at least two of the following: abdominal pain; serum lipase ≥3 times the upper limit of normal (ULN) or a value of 300 U/L or higher without a specified normal range or serum amylase ≥5 times ULN or a value of 1000 U/L or higher without a specified normal range; and magnetic resonance imaging (MRI) or computed tomography (CT) scan with interpretation of peripancreatic fluid collection or streaking, or pancreatic edema or necrosis. These investigators also abstracted a random sample of medical records of patients with CPT codes for amylase or lipase tests (CPT 82150 or 83690) associated with an inpatient or Emergency Department (ED) encounter, but without a diagnosis code for acute pancreatitis, to assess the sensitivity of the claims-based case screening. They found an overall PPV for the ICD-9 code 577.0 in any position to be 50%, and in the first position to be 60%. They also found that the PPV varied by age group in the sample of 409 records with the ICD-9 code in the first position. For those less than 40 years of age the PPV was 74%, from 40-54 years of age it was 63%, from 55-64 years of age it was 57%, and greater than 65 years of age it was 51%. However, the 95% confidence intervals for these PPVs showed obvious overlapping. Of the 156 medical records obtained of patients with a CPT code for amylase or lipase tests without an ICD-9 code for pancreatitis none had confirmed acute pancreatitis.

Two validation studies have been published as abstracts only. One study involved a population of veterans in which ICD-9 codes 577.0 and 577.1 were validated.[15] The other involved patients with a primary discharge diagnosis acute pancreatitis ICD-9 code 577.0 at two University of Pittsburgh Medical Center hospitals.[16] PPVs in the Veteran's Administration (VA)and University of Pittsburgh studies were approximately 65% and approximately 77%, respectively. Both studies found a negative predictive value of approximately 97%.

A description of two non-validated algorithms is included in the evidence table below because they demonstrate that the most frequently validated algorithm of the ICD-9 code of 577.0 has in one case been used in a very large inpatient care database by Brown, et al.[17] This report provides some potentially useful evidence of the increasing incidence of acute pancreatitis and other demographic characteristics of patients diagnosed with this disease. The other report, by Dore, et al., demonstrates

the use of ICD-9 code 577.0 in a large database to examine the incidence of pancreatitis associated with the use of selected medications for the treatment of diabetes. [18]

G. SUMMARY OF EXCLUDED POPULATIONS AND DIAGNOSES

As described in section F above, collectively the studies included few restrictions beyond the general selection of populations of interest. They ultimately provided reasonably representative data for the primary patient characteristics of interest in the incidence of pancreatitis. Half of the studies examined specific higher-risk populations that make the findings somewhat difficult to generalize to a larger population. These included veterans with an alcohol use disorder in an outpatient detoxification program,[8] Ohio Medicaid patients less than 65 years of age with HIV and a prescription for an antiretroviral,[9] and patients in a single health care system who were initiated on dialysis.[13] Of three studies that examined pancreatitis in populations not restricted to particular disease states or higher-risk groups, two were from single tertiary care medical centers,[10,12] one of which only included patients 21 years of age and younger. The other study included patients in the Kaiser Permanente Medical Care system of San Francisco and Oakland.[11]

H. EVIDENCE TABLES

Table 3. Positive Predictive Values by Algorithm

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure and Operational Definition, and Validation Statistics
Yadav D et al. 2007 [8]	Male veterans attending the outpatient detoxification program at the Central Arkansas Veterans Healthcare System. January 2002 to December 2003. A total of 1409 patients were treated in this program during this time period. Patients with gallstones were excluded. All subjects in the sample had and ICD-9 diagnosis code for alcohol abuse. The mean age was 47.6 years, 43.6% were white, 90% had drug use at some time, 90% were current smokers, 27% had hepatitis C.	The objective of this study was to determine the prevalence and risk factors for pancreatitis in a population of heavy-drinking male veterans in a detoxification program. The prevalence of pancreatitis (either acute or chronic) in this population was found to be 3%. Alcohol was considered the cause in 39 of 42 cases.	ICD-9 code 577.0 for acute pancreatitis or ICD-9 code 577.1 for chronic pancreatitis	The medical record for all 87 patients with an ICD- code for pancreatitis, and a random sample of 214 subjects without the ICD-9 code, were reviewed by the study gastroenterologist who was blinded to the code. Confirmation of acute pancreatitis (AP) was based on the presence of typical abdominal pain with elevation of amylase and/or lipase 3 times or more than normal and/or imaging evidence of pancreatitis. Alcoholic chronic pancreatitis (CP) was confirmed based on 1) typical history of recurrent episodes of AP, except primary painless CP, 2) history of excessive alcohol intake ≥ 80 g/day for some years in males plus one of the following: a) calcification in the pancreas (x-ray or CT), b) moderate or marked changes in ductal system on ERCP, c) marked exocrine insufficiency, d) typical histology on adequate surgical specimen. Chart review verified 40 of the 87 patients with an ICD-9 code for pancreatitis- PPV 46% For patients with both codes 577.0 and 577.1 the PPV was 77%, for code 577.0 only it was 40%, and for code 577.1 only it was 20%. Of the 214 patients without an ICD-9 code for pancreatitis 2 had chronic pancreatitis confirmed by chart review. NPV 99%.
Guo JJ et al. 2005 [9]	Ohio Medicaid patients with a diagnosis of HIV and at least one prescription for an antiretroviral medication. N=4972 January 1997 to December 2002. Mean age 36.1 ± 10.7, 27% female, 48% were Caucasian, 44% were African	Assess the risk of acute pancreatitis in patients receiving combinations of protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTI) and nonnucleoside	ICD-9 code 577.0 and at least one lab order for either amylase or lipase indicated by CPT codes 82150 or 83690 within 30 days before or after the date of diagnosis	Random sample of 20 patients with acute pancreatitis had their inpatient and outpatient medical claims records reviewed. The record was examined for at least one sign or symptom of nausea, vomiting, abdominal pain, or tenderness accompanied by elevation of serum amylase or lipase level. ICD-9 for nausea or vomiting 787.03, 789.0 for abdominal pain, 789.60-789.69 for abdominal tenderness. They also expected discontinuation of one or both NRTIs or protease inhibitors or a switch in

	American, 10% had diabetes, 44% had a preexisting mental illness

Excluded patients ≥65 yrs | reverse transcriptase inhibitors for treatment of HIV infection | | antiretroviral drugs.

NOT REPORTED. The validation process was described in the methods but no results were reported. The lead author was contacted to request information on these results, but none was received. |
| McMenamin 1996 [10] | All patients from University of Kentucky Chandler Medical Center in 1992 with discharge ICD-9 code 577.0, n= 115. Mean age 42, 56% male, etiology of pancreatitis: alcohol 17, unknown 21, ERCP 9, drug 3, stone 3, hyperlipidemia 2, malignancy 2. 6 deaths occurred. | Effect of contrast enhanced CT on the outcome of acute pancreatitis | ICD-9 code 577.0 in discharge records | Medical records were available for 95 of the 115 cases and were reviewed for clinical evidence of pancreatitis. Clinical evidence included abdominal pain with an assessment noted of pancreatitis in the progress notes, serum amylase > 2X the upper limit of normal, and possibly an inability to tolerate a normal diet, but this is not stated clearly. These were the factors used in the study to document duration of the episode of acute pancreatitis.

22 of 95 cases had a lack of documented clinical evidence of pancreatitis 73/95 PPV= 76.8%. The authors did not report PPV, only the exclusion of 22 patients from the study for lack of clinical evidence of pancreatitis. |
| Morton C 2004 [11] | Baseline data from 1978 to 1985 of 128,934 adults in the Kaiser Permanente Medical Care in San Francisco and Oakland. Records screened to 12-31-1998. 50% men, 48.5% < 50 years of age, 35 % were black, 51% were white or Hispanic, 7.5% Asian. | The purpose of the study was to examine a possible relationship of coffee and smoking with pancreatitis. | Hospitalization for possible pancreatitis was screened for a primary discharge diagnosis with code 577.x | A trained medical record analyst performed initial chart screening with a physician investigator reviewing all final diagnoses. A diagnosis of pancreatitis was considered confirmed if symptoms and physical examination were compatible and the serum amylase was elevated. In cases without elevated serum amylase evidence of pancreatitis by imaging or direct examination of the organ was required.

452 persons were initially screened, 439 were confirmed to have pancreatitis. PPV was not reported by the authors but it is 97% based on the data reported. This study did not distinguish between acute or chronic pancreatitis. |
| Park A 2009 [12] | Yale-New Haven Children's Hospital, New Haven, CT tertiary care teaching hospital with a broad catchment area. Patients age birth to 21 years seen between August 1994 and July 2007. Mean age 13.1 ± 5.64, 40% male, 53% white, 23% | The study was performed to examine the frequency of acute pancreatitis in a pediatric population from 1994 to 2007 and to characterize etiologies by age subsets. | ICD-9 code for acute pancreatitis, not stated but assumed to be 577.0. | Records were reviewed for inclusion criteria relevant to acute pancreatitis. To be included in the study group, patients needed any 1 of the following 3 features:

1. Serum amylase or lipase greater than 3 times the upper limit of normal

2. Radiographic evidence of acute pancreatitis on computed tomography (CT) and ultrasound (U/S) demonstrating a minimum of pancreatic parenchymal |

				changes or peripancreatic fluid
	black, 19% Hispanic. The most common causes of acute pancreatitis were biliary 32.6%, medications 25.6%, idiopathic 20%, systemic 10%, trauma 9%, viral infection 8%,5% metabolic condition, 4% ERCP			3. Serum lipase greater than 1.5 times the upper limit of normal that could not be explained by nonpancreatic causes of hyperlipasemia, and the presence of 2 out of 3 clinical features—abdominal pain characteristic of acute pancreatitis, nausea and vomiting, or epigastric tenderness 282 patients were identified by ICD-9 codes. 215 met the inclusion criteria of a confirmed case of pancreatitis. 18 were excluded as chronic pancreatitis. The others had incomplete data. 215/282 is a PPV of 76.2%. PPV was not calculated by the authors.
Quraishi ER et al. 2005 [13]	Patients in the Henry Ford Health System (HFHS) in Detroit who were initiated on dialysis after January 1, 1998. Data were collected retrospectively from January 1, 1998 to August 1, 2003.	Compare the incidence of acute pancreatitis in ESRD patients on peritoneal dialysis and hemodialysis.	ICD-9 codes for pancreatitis and pancreatitis-related complications in the admitting and discharge diagnoses. The following ICD-9 codes were used: 577.0, 577.1, and 577.2.	AP is defined by presence of abdominal pain in association with elevation of serum amylase and/or lipase more than three times the upper limit of normal and the absence of any other clinical syndrome that could produce a similar clinical presentation. Electronic medical records and paper charts were reviewed. 128 patients were identified by ICD-9 codes for AP and AP-related complications. No information about abdominal symptoms or elevated enzyme levels were found for 80 patients, 14 had cholecystitis with no evidence of AP, and 6 had diabetic ketoacidosis with no evidence of AP. 28 met criteria for AP; a PPV of 22%. 107 patients without ICD-9 codes for pancreatitis but with elevated amylase or lipase were found in electronic records. Manual chart review found that none met criteria for AP. The authors did not report specific performance statistics of the algorithm. It is unclear if the use of multiple ICD-9 codes had been included in order to produce high sensitivity at the expense of specificity of the algorithm. That appears to be true, but the authors did not address this issue or report which ICD-9 codes were most commonly reported
Dore et al. 2011[14]	Initiators of antihyperglycemic drugs between 6-1-2005 and 12-31-2007, in the Normative Health Information (NHI) database.	Validate ICD-9 code of 577.0	ICD-9 code 577.0 for acute pancreatitis in first position, or in any position, of an emergency department or	PPV for 577.0 in any position was 50% PPV for 577.0 in first position was 60% PPV based on age in the sample with 577.0 in the first position ranged from 51% in the oldest group to 74% in the

	Female 50%; age <40years 19.2%, age 40-54 37.8%, age 55-64 30.9%, age 65+ 12.1%. Type 2 DM 61.5%.		hospitalization claim	youngest group.
Yadav D et al. 2006 [15]	All male veterans with any pancreatitis ICD-9 codes (577.0 or 577.1) at the Little Rock AR VA between January 2001 and December 2002 Plus 300 random controls without pancreatitis codes in the same period	Validate pancreatitis codes in male veterans	ICD-9 code 577.0 for acute pancreatitis or ICD-9 code 577.1 for chronic pancreatitis	Acute pancreatitis was verified in the medical records by the presence of typical abdominal pain with ≥3 times elevation in serum amylase or lipase or imaging evidence of pancreatitis. Chronic pancreatitis was verified per 1997 International workshop on CP Pancreas 1997;14:215-21. The PPV for verified pancreatitis was 63% in the 418 patients with a pancreatitis code. The negative predictive value of no pancreatitis code was 98%
Saligram S et al. 2010 [16]	All unique patients (n=391) who received a primary discharge diagnosis of AP (ICD9-577.0) for the first time after inpatient admission through the emergency room (ER) in years 2000, 2002 and 2005 at two University of Pittsburgh Medical Center hospitals (University [UH], n=200 and community [CH], n=191). Each patient was matched to the closest control (n=391) Median age 54, 50% male, 84% Caucasian.	Determine the validity of the diagnosis code for AP	ICD-9 code 577.0	Medical records were reviewed for the presence of characteristic abdominal pain with ≥3x elevation of amylase and/or lipase or imaging evidence of AP as the "Gold standard" for AP diagnosis. Two traditional etiologies, i.e., gallstones and alcohol were present in 34% and 14% cases respectively. For all cases of AP the PPV was 77% and a NPV in controls was determined to be 97%

Table 4. Non-Validated Algorithms

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm
Brown A, et al. 2008 [17]	The National Inpatient Sample (NIS) database is the largest all-payer inpatient care database in the U.S. The database contains discharge data from 994 hospitals representing 37 states. The hospitals which provide data to the NIS represent a stratified sample of 20% of all U.S. community hospitals. This study covered the period 1997-2003. Mean age 52.6, male 51.0%. During the study period there were 1,476,498 admissions with a principal discharge diagnosis of acute pancreatitis. The frequency of AP discharges increased by 30.2% from 1997-2003. Most discharges with AP were in the Southern US and were at large non-teaching hospitals located in urban areas.	Acute pancreatitis ICD-9 code 577.0 as the principle discharge diagnosis Patient demographics show that 51% are male, 1.6% are age 1-17 years, 35.6% 18-44 years, 34.8% 45-64 years, 23.3% 65-84 years and 4.7% 85+ years. The mortality rate declined from approximately 1.9% in 1997 to 1.4% in 2003. The mean length of stay declined from 6.4 days to 5.8 over this period.	577.0 (acute pancreatitis)
Dore et al. 2009 [18]	Data were obtained from the proprietary Ingenix Research Datamart (RDM) from June 2005 through June 2008. 27,996 initiators of exenatide, 44,264 initiators of metformin/glyburide, 16,276 initiators of sitagliptin. Age range from less than 19 to over 60, 40% were 50-59, approximately 50% female.	Acute pancreatitis based on hospitalization claims with a primary ICD-9 diagnosis code of 577.0	577.0 (acute pancreatitis)

I. CLINICIAN OR TOPIC EXPERT CONSULTATION

The current ICD-9-CM terminology code for acute pancreatitis (577.0) entered circulation in 1977. The clinical diagnostic criteria for the assessment of acute pancreatitis have remained stable for the past 3 decades, largely relying on three components: history, laboratory, and radiology exam. The key historical elements are: 1) history of acute onset of mid-epigastric pain, 2) with radiation to the back, 3) combined with the presence of either nausea or vomiting and 4) aggravation by oral consumption. Key laboratory elements include elevations (>3x normal) of amylase and/or lipase. Finally, in cases where the clinical history or laboratory examination is uncertain, computed tomography of the abdomen revealing pancreatic inflammation can secure the diagnosis.

The current ICD-9-CM code for acute pancreatitis (577.0) refers to *"acute or chronic inflammation of the pancreas due to auto-digestion of the pancreatic tissue by its own enzymes", "inflammation of the pancreas with pain as the primary symptom".* This definition also covers other associations or etiologies of the pancreatic inflammation such as hemorrhagic, annular, apoplectic, calcareous, gangrenous, acute

interstitial, malignant, suppurative, and subacute. Thus, the major limitation of the current 577.0 terminology does not allow for etiological or a pathophysiological description of the kind of acute pancreatitis, a clear difference between ICD-9 and ICD-10 coding algorithms. Consideration of this must be given weight because, as of the year 2013, physicians will be required to code using ICD-10 terminology.

Studies validating acute pancreatitis using 577.0 indicated a range of PPV from 40 – 70%.[8,10] For the most part these studies relied on chart abstraction methods and used screening personnel (e.g., research assistant) confirmed by an expert reviewer (e.g., physician or gastroenterologist). The information abstracted was consistent with clinical criteria but in several cases poor medical charting limited the studies' ability to find higher PPV for the algorithm.

There was only one study that attempted to validate chronic pancreatitis using 577.1, which found a PPV of 20%. Combining the lack of clinical agreement on diagnosing chronic pancreatitis with the lack of studies specifically examining the validity (or added sensitivity and specificity) of 577.1, the use of this code is not recommended. Use of code 577.2 is also not recommended based on similar reasoning.

Identifying incident cases of acute pancreatitis should be relatively straightforward as most cases of 577.0 will be recorded on a hospital discharge, and screening for prior primary and secondary codes for 577.0 in a population over period of time should be feasibly accomplished. The main difficulty will be identifying populations at risk for the development of acute pancreatitis due to reasons other than exposures under study, such as heavy alcohol users without a diagnosis of alcohol abuse or dependence.

Further study is warranted to determine the value of using procedure codes as part of the coding algorithm to determine the presence of acute pancreatitis in the absence of 577.0 but with either 577.1 – 577.2. In such cases the presence of a CPT code for amylase or lipase, or the receipt of an abdominal CT scan with peri-pancreatic findings, could both enhance PPV and maintain specificity.

VI. SUMMARY AND CONCLUSIONS

A. RECOMMENDATIONS FOR ALGORITHMS

Studies that included a primary hospital discharge diagnosis of ICD-9 code 577.0 appeared to have the best PPV and specificity. The additional inclusion of 577.1 and 577.2 does not have sufficient literature support to recommend their use at this time.

B. SUGGESTIONS FOR FUTURE RESEARCH BASED ON EVIDENCE GAPS

Due to the variability in performance characteristics identified and single center nature of most studies, it may be useful to perform validation studies that use case finding algorithms from large administrative databases encompassing broad population bases. In particular, focusing on databases that are enhanced with actual laboratory data gathered at point of admission (e.g., VA hospital data using linked laboratory data) could lend additional confidence in selecting the best algorithm. Performance characteristics seemed to vary, somewhat unpredictably, among studies of groups with different baseline risks of pancreatitis. This is a notable limitation in the current studies since most populations were defined by a unique illness (e.g. HIV or ESRD) or to be contained within a specific healthcare system. Finally, algorithms have not been validated in the very elderly and validation studies have not been performed with ICD-10 codes.

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VIII. APPENDICES

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

1. Validation Studies Included in the Evidence Table

Guo JJ, Jang R, Louder A, Cluxton RJ. Acute pancreatitis associated with different combination therapies in patients infected with human immunodeficiency virus. *Pharmacotherapy*. 2005; 25: 1044-1054.

STUDY OBJECTIVE: To assess the risk of acute pancreatitis in patients receiving various combinations of protease inhibitors, nucleoside reverse transcriptase inhibitors (NRTIs), and nonnucleoside reverse transcriptase inhibitors (NNRTIs) for treatment of human immunodeficiency virus (HIV) infection. DESIGN: Retrospective cohort study. DATA SOURCE: Ohio Medicaid claims database, January 1997-December 2002. PATIENTS: Four thousand nine hundred seventy-two patients with HIV infection who had received at least one antiretroviral drug. MEASUREMENTS AND MAIN RESULTS: Three combination regimens were evaluated: didanosine plus other antiretroviral agents, protease inhibitors plus NRTIs or NNRTIs, and NRTI combinations (no didanosine) or NRTIs plus NNRTIs. We used Cox proportional hazard regression and Kaplan-Meier plots to examine the risk for acute pancreatitis. We identified 159 (3.2%) cases of acute pancreatitis during the study period. For patients who were newly treated for HIV, the incidence of acute pancreatitis was 1.95/100 person-years. Half of these cases developed within 500 days of the start of drug therapy. Hazard ratios (HRs) for acute pancreatitis were 39-54% higher for nonwhite patients than Caucasians and 240-290% higher for symptomatic versus nonsymptomatic patients. Hazard ratios also were significantly associated with increased age, liver injuries (HR 2.94, 6.73), and cardiovascular diseases (HR 1.68, 2.36), respectively, for both newly treated and previously diagnosed patients with HIV. The risk for patients receiving either protease inhibitors plus an NRTI or an NNRTI, or NRTI plus NNRTI combinations was not significantly different from the risk associated with didanosine combination therapy (p>0.10). CONCLUSION: The risk of acute pancreatitis was significantly associated with age, race, symptomatic HIV infection, and liver and cardiovascular diseases. However, risk did not differ significantly among patients with different antiretroviral regimens. Our results can be used by the medical community to enhance patient safety and minimize costly adverse drug reactions among patients with HIV infection.

McMenamin DA, Gates LK,Jr. A retrospective analysis of the effect of contrast-enhanced CT on the outcome of acute pancreatitis. *Am J Gastroenterol*. 1996; 91: 1384-1387.

OBJECTIVES: Contrast CT is widely used to assess the severity of acute pancreatitis. Recently, studies in rats have shown that the administration of i.v. contrast material worsens the outcome of experimental acute pancreatitis. The aim of the current study was to determine if an effect of the administration of i.v. contrast could be identified in clinical acute pancreatitis. METHODS: Charts from the University of Kentucky Hospital from 1992 with an ICD-9 code of acute pancreatitis were reviewed. APACHE II scores at diagnosis of pancreatitis were calculated for all patients. The duration of clinical pancreatitis was determined from the date of onset of pain to the date of resolution of pain and resumption of oral nutrition. Contrast CT and noncontrast groups were compared using a Mann-Whitney rank sum test. RESULTS: There was no significant difference in the original APACHE II scores between the two groups. The contrast CT group had a mean duration of clinical pancreatitis of 10.8 days versus 6.2 days for the non-CT group (p = 0.004). CONCLUSIONS: This retrospective study supports the conclusions of recent animal studies that suggest that i.v. contrast might worsen or prolong attacks of acute pancreatitis.

Morton C, Klatsky AL, Udaltsova N. Smoking, coffee, and pancreatitis. *Am J Gastroenterol*. 2004; 99: 731-738.

OBJECTIVES: We studied relationships of cigarette smoking and coffee drinking to risk of pancreatitis. METHODS: This was a cohort study among 129,000 prepaid health plan members who supplied data about demographics and habits in 1978-85. Among 439 persons subsequently hospitalized for pancreatitis, probable etiologic associations were cholelithiasis (168/439 = 38%), alcohol (125/439 = 29%), idiopathic (110/430 = 25%), and miscellaneous (36/439 = 8%). Cox proportional hazards models with seven covariates (including alcohol intake) yielded relative risk estimates for smoking and coffee use. RESULTS: Increasing smoking was strongly related to increased risk of alcohol-associated pancreatitis, less related to idiopathic pancreatitis, and unrelated to gallstone-associated pancreatitis. Relative risks (95% confidence intervals, CI) of one pack per day (vs never) smokers for pancreatitis groups were: alcohol = 4.9 (2.2-11.2, p < 0.001), idiopathic = 3.1 (1.4-7.2, p < 0.01), and gallstone = 1.3 (0.6-3.1). The relationship of smoking to alcohol-associated pancreatitis was consistent in sex and race subsets. Drinking coffee, but not tea, was weakly inversely related to risk only of alcohol-associated pancreatitis, with relative risk (95% CI) per cup per day = 0.85 (0.77-0.95; p= 0.003). Male sex, black ethnicity, and lower-educational attainment were other predictors of alcohol-associated pancreatitis. CONCLUSIONS: Cigarette smoking is an independent risk factor for alcohol-associated and idiopathic pancreatitis. Coffee drinking is associated with reduced risk of alcohol-associated pancreatitis. The data are compatible with the hypotheses that smoking may be toxic to the pancreas or may potentiate other pancreatic toxins while some ingredient in coffee may have a modulating effect.

Park A, Latif SU, Shah AU, et al. Changing referral trends of acute pancreatitis in children: A 12-year single-center analysis. *J Pediatr Gastroenterol Nutr*. 2009; 49: 316-322.

BACKGROUND: Acute pancreatitis is a painful inflammatory disorder known to occur in children. Recent reports, primarily on the basis of adult data, have suggested an increasing incidence. However, pediatric studies are limited. OBJECTIVE: The study was performed to examine the frequency of acute pancreatitis in a pediatric population from 1994 to 2007 and to characterize etiologies by age subsets. PATIENTS AND METHODS: In this retrospective study, cases of pancreatitis were identified by ICD-9 codes and subjected to inclusion criteria. RESULTS: Two hundred and seventy-one cases of pancreatitis met inclusion criteria. Mean age of the subjects was 13.1 +/- 5.6 years. The recurrence rate was 15.3%. Biliary disease was the most common etiology (32.6%). Acute pancreatitis cases evaluated at a single tertiary care center increased 53% between 1995 to 2000 and 2001 to 2006 (P < 0.02). However, when cases were normalized by all annual pediatric emergency department visits for all medical reasons, the increase was reduced to 22% and lost statistical significance (P = 0.16). The rise was not associated with a change in etiologies or body mass index (BMI). CONCLUSIONS: This is the first report demonstrating that an increase in pediatric pancreatitis may in part be due to growing referrals to tertiary care centers. The data on etiologies, particularly with regard to differing ages, may be helpful in managing children who present with acute pancreatitis.

Quraishi ER, Goel S, Gupta M, Catanzaro A, Zasuwa G, Divine G. Acute pancreatitis in patients on chronic peritoneal dialysis: An increased risk? *Am J Gastroenterol*. 2005; 100: 2288-2293.

OBJECTIVES: The primary aim of this study is to determine if patients with end-stage renal disease (ESRD) on peritoneal dialysis (PD) have a higher risk of developing acute pancreatitis (AP) than patients on hemodialysis (HD). The secondary aim is to compare the outcomes of AP between the

two groups. METHOD: This is a retrospective case-control study. The study groups consisted of all patients initiated on HD and PD between January 1, 1998 and August 1, 2003. AP was identified using ICD-9 codes. Statistical analysis was carried out using Poisson regression, Kaplan-Meier curve, log-rank test, and Cox regression. RESULTS: One thousand two hundred and thirty-three and 160 eligible patients were identified in the HD and PD groups, respectively. Twenty-eight patients had AP. Eight patients were excluded as they had identifiable etiologies for AP. Of the remaining 20 patients with AP, 14 were in the HD group and 6 were in the PD group (p= 0.009). Incidence of AP was 18.4 per 1,000 person-years in the PD group and 6.5 per 1,000 person-years in the HD group (p= 0.033). Kaplan-Meier curves showed a significant difference in AP-free survival between the two groups (log-rank p= 0.026). Using time-dependent analysis, the hazard ratio for AP in PD patients after adjustment for age and sex was 3.94 (p= 0.006). There was no observed difference in length of hospital stay and ICU stay. All cases of AP were interstitial. There were no complications or deaths related to AP. CONCLUSION: PD is a risk factor for AP. There is no statistical difference in AP-related mortality and morbidity between HD and PD.

Yadav D, Eigenbrodt ML, Briggs MJ, Williams DK, Wiseman EJ. Pancreatitis: Prevalence and risk factors among male veterans in a detoxification program. *Pancreas*. 2007; 34: 390-398.

OBJECTIVES: To determine the prevalence of pancreatitis and associated risk factors among heavy-drinking veterans. METHODS: At a large Veterans Administration Outpatient Detoxification Program (ODP) that systematically collects risk information, 1409 black and white male veterans with International Classification of Diseases, Ninth Revision codes for alcohol abuse enrolling in the ODP from January 2002 to December 2003 were identified. Among these patients, pancreatitis at any time (before the ODP admission or occurring through June 2005) was identified using International Classification of Diseases, Ninth Revision codes. Cases were verified by chart review. Logistic regression analyses were used for multivariable analyses. RESULTS: Overall, history of smoking (89.6%) and current or past drug use (90.1%) were very common, whereas intravenous drug use (22.3%) was less so. Although 87 (6.2%) subjects had pancreatitis codes (acute, 50; chronic, 15; both, 22), chart review verified only 42 cases (acute, 29; chronic, 5; both, 8) for a 3% prevalence. Alcohol appeared to be the definite etiology in 39 of these 42 patients. In bivariate analyses, patients with pancreatitis were older, had more substance abuse admissions, reported a significantly heavier current alcohol use, and lower drug dependence (each P < 0.05). In multivariable models, alcoholic pancreatitis was associated positively with age (odds ratio, 1.08; 95% confidence interval, 1.04-1.12) and number of substance abuse admissions (odds ratio, 1.08; 95% confidence interval, 0.995-1.18; P = 0.06). CONCLUSIONS: In this high-risk population of heavy drinkers, the prevalence of pancreatitis is at least 3%. Our study provides preliminary data regarding potential cofactors for pancreatitis in heavy drinkers.

Dore DD, Chaudhry S, Hoffman C, Seeger JD. Stratum-specific positive predictive values of claims for acute pancreatitis among commercial health insurance plan enrollees with diabetes mellitus. *Pharmacoepidemiol Drug Saf*. 2011; 20: 209-13.

PURPOSE: To estimate the positive predictive value (PPV) of claims for acute pancreatitis among initiators of antihyperglycemic drugs in commercial health insurance claims data. METHODS: As part of a systematic study of the occurrence of acute pancreatitis among antihyperglycemic drug initiators (N=260,255) within a large US health insurer's claims database, we identified potential cases of acute pancreatitis and confirmed them through medical record review. Potential cases had an International Classification of Diseases, 9th revision diagnosis code for acute pancreatitis (577.0) associated with an inpatient or emergency department claim. We sought 860 medical records to

confirm potential cases and received 585 (70%), which were reviewed by a clinical adjudication committee. We estimated the PPV and 95% confidence intervals (CI) of claims for these medical records and a subset that had the diagnosis code listed in the first position of an inpatient claim. RESULTS: The PPV was 0.50 (95% CI 0.44-0.53) for an acute pancreatitis diagnosis code in any position and 0.60 (95% CI 0.55-0.65) if in the first position of an inpatient claim. The estimated PPV varied across strata defined by patient characteristics and was generally lower within strata where potential risk factors for acute pancreatitis were present. CONCLUSIONS: These data indicate that health insurance claims-based identification of acute pancreatitis might overestimate actual cases and introduce appreciable bias, usually toward the null. Further case confirmation or relative risk correction may be necessary to address potential bias.

Yadav D, Dhir R. How accurate are ICD-9 Codes for acute (AP) and chronic (CP) pancreatitis? A large VA hospital experience. *Pancreas*. 2006; 33: 508.

Background and Aims: Administrative data is increasingly used to study many disease outcomes. Data on validity of AP diagnosis code is limited, while none exist for CP code. Our aim was to validate pancreatitis codes in male veterans receiving ICD-9 codes for pancreatitis during 2001-2 at our VA hospital. Methods: All male veterans receiving any pancreatitis ICD-9 codes (AP- 577.0, CP-577.1) between 1/2001-12/2002 at our VA Hospital were identified using the computerized V A database. The records of all subjects with pancreatitis codes (n = 418) and 300 random controls without pancreatitis codes during study period [equal number of i) inpatients with diseases in the differential diagnosis of pancreatitis, ii) inpatients for any reason, and iii) outpatients] were reviewed in a blinded fashion. To verify pancreatitis we used criteria ranging from definite cases (AP-typical abdominal pain with 2:3 times enzyme elevation or imaging evidence of pancreatitis, CP- per 1997 International workshop on CP: *Pancreas* 1997;14:215-21) to probable cases (clinically suspected but not fulfilling strict criteria). Diagnosis was verified at an individual level (i.e., whether having a pancreatitis code indicates true pancreatitis in a given patient) - during study period or at anytime. Results: Verified pancreatitis (definite or probable) at anytime was present in 63% patients with pancreatitis codes (AP-I64, CP-10, both-89) and 3% controls (AP-6, both AP and CP-3). The commonest etiology was alcohol use for both AP (itself or present with other etiologies in 53%) and CP(89%). The PPV were mostly similar after stratification of data for race (blacks vs whites) and for history of alcohol use (yes or no).Conclusions: Although pancreatitis codes have high sensitivity and NPV, their specificity and PPV is only low-moderate indicating a large number of false-positives (approx. one-third). This finding has implications when interpreting administrative data alone without a chart review. Validation studies in different populations and predictive modeling for diagnosis and etiology are needed if administrative data alone is to be used or planned to study long term outcomes in pancreatitis.

Saligram S, Lo D, Saul M, Sanders M, Papachristou G, Yadav D. Validity of Administrative Data for Acute Pancreatitis. *Am J Gastroenterol*. 2010; 105(suppl 1): S62.

Purpose: Numerous recent studies have used administrative data to describe the epidemiology and outcomes in acute pancreatitis (AP). However, there are scarce data on validity of administrative code for AP. Our aim was to determine the validity of the diagnosis code for AP. Methods: We identified all unique patients (n=391) who received a primary discharge diagnosis of AP (ICD9- 577.0) for the first time after inpatient admission through the emergency room (ER) in years 2000, 2002 and 2005 at two University of Pittsburgh Medical Center hospitals (University [UH], n=200 and community [CH], n=191). Each patient was matched to the closest control (n=391) by age, gender, race, year of admission, ICU admission and whether abdominal CT was done. Controls were chosen

from patients who presented to the ER for abdominal pain, underwent serum amylase and/or lipase estimation and discharged after inpatient admission without a primary or secondary diagnosis of any pancreatitis. Medical records were reviewed to obtain information on demographic, clinical, radiology and outcomes data. We used presence of characteristic abdominal pain with ≥3x elevation of amylase and/or lipase or imaging evidence of AP as the "Gold standard" for AP diagnosis. For each year, we determined the proportion of ER visits where serum pancreatic enzymes were estimated. Results: Controls and AP cases were similar in age (median 54 vs 53 years), gender (48 vs 50% male), race (85 vs 83% Caucasian), ICU admission (7 vs 6%) and whether CT was done (67 vs 65%) (all p-values- NS). The two traditional etiologies, i.e., gallstones and alcohol were present in 34% and 14% cases respectively. Prior history of any pancreatitis was present in 56/391 (14%) cases. Pancreatic necrosis was seen in 14/391 (4%) cases. Gold standard for AP diagnosis was fulfilled in 300/391 (77%) cases (≥3x enzyme elevation-71%; positive CT or USG-36%). Pancreatic enzyme elevation among controls was uncommon (1-2x N- 11% 2-3x N- 3%; >=3x N- 2%). Predictive value for AP diagnosis code is shown in Table 1. PPV was the highest (83%) among patients who presented to the ER within 12 hours of onset of abdominal pain. Overall, predictive values were similar at the two hospitals. Subset analysis indicated a decrease in PPV for diagnosis code over time at the CH (PPV 93% in 2000; 70% in 2005), which negatively correlated (r=-0.98) with the proportion of all ER visits where estimation of serum pancreatic enzyme testing was performed (7.7% in 2000; 12% in 2005). Conclusion: The diagnosis code for AP is valid especially when unique patients without prior attacks of pancreatitis are chosen. Careful selection of AP patients from administrative datasets can serve as a valid methodology for outcomes studies in AP.

2. Non-Validation Studies Included in the Evidence Table

Brown A, Young B, Morton J, Behrns K, Shaheen N. Are health related outcomes in acute pancreatitis improving? An analysis of national trends in the U.S. from 1997 to 2003. *JOP*. 2008; 9: 408-414.

> CONTEXT: Acute pancreatitis is a common inflammatory disorder of the pancreas. Within the past decade our ability to diagnose and treat complications of acute pancreatitis has improved. Despite advances in diagnostic and therapeutic technology it is unclear whether we have been able to impact health related outcomes of acute pancreatitis such as incidence and mortality. OBJECTIVE: The aim of this study was to use a national database of U.S. hospitals to evaluate the trends in the incidence and mortality associated with acute pancreatitis. We also examined the impact that patient demographic and hospital characteristics have on health related outcomes in acute pancreatitis. METHODS: We analyzed the National Inpatient Sample Database (NIS) for all subjects in which acute pancreatitis (ICD-9 code: 577.0) was the principal discharge diagnosis during the period from 1997-2003. All identified subjects were analyzed for demographic characteristics as well as hospital characteristics. MAIN OUTCOME MEASURES: The mean frequency of discharges for acute pancreatitis, percentage mortality and mean length of stay for acute pancreatitis were determined for all identified cases. STATISTICS: The statistical significance of the difference in the discharge frequency, mortality and length of stay over the study period was determined by utilization of the chi-square test for trend and the linear regression. RESULTS: During the study period there were 1,476,498 admissions with a principal discharge diagnosis of acute pancreatitis. The frequency of discharges with acute pancreatitis increased by 30.2% (P<0.001) during the period from 1997-2003. The average mortality associated with acute pancreatitis decreased by 35.2% (P<0.001) and the median length of stay decreased by 9.4% (P=0.002). Most discharges with acute pancreatitis were in the Southern U.S. and were at large non-teaching hospitals located in urban areas. DISCUSSION:

Possible explanations for the results of our study are the improvements in our ability to diagnose acute pancreatitis, an increase in the availability of medical ICU's and an increase in hospital admissions for gallstones and alcohol use during the study period.

Dore DD, Seeger JD, Arnold Chan K. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin*. 2009; 25: 1019-1027.

OBJECTIVE: To estimate risk and relative risk (RR) of acute pancreatitis among patients using incretin-based diabetes therapies (exenatide or sitagliptin) compared to patients treated with agents with established safety profiles (metformin or glyburide). RESEARCH DESIGN AND METHODS: The study population was derived from a large US commercial health insurance transaction database using an active drug safety surveillance system (i3 Aperio). This analysis is based on data from June 2005 through June 2008. Cohorts of exenatide and sitagliptin initiators were each matched to an equal number of metformin or glyburide (met/gly) initiators using propensity scores to reduce confounding in the comparison of outcomes during follow-up. Patients with claims suggesting pancreatic disease in the 6 months prior to cohort entry were excluded. MAIN OUTCOME MEASURE: Claims for hospitalizations associated with a primary diagnosis of acute pancreatitis (ICD-9 577.0). RESULTS: There were 27 996 exenatide initiators and 16 276 sitagliptin initiators and approximately equal numbers of matched comparators. During follow-up of up to 1 year, acute pancreatitis occurred among 0.13% of patients treated with exenatide and 0.12% of patients treated with sitagliptin. The risk of acute pancreatitis was comparable for initiators of exenatide (RR 1.0; 95% confidence interval (CI) 0.6-1.7) and sitagliptin (RR 1.0; 95% CI 0.5-2.0) relative to the comparison cohorts. CONCLUSIONS: These data do not provide evidence for an association of acute pancreatitis among initiators of exenatide or sitagliptin compared to met/gly initiators. These results are limited by the data available in an administrative, healthcare database.

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

Buscaglia JM, Kapoor S, Jagannath SB, Krishnamurty DM, Shin EJ, Okolo PI,3rd. Disparities in demographics among patients with pancreatitis-related mortality. *JOP*. 2009; 10: 174-180.

Cannon GW, Holden WL, Juhaeri J, Dai W, Scarazzini L, Stang P. Adverse events with disease modifying antirheumatic drugs (DMARD): A cohort study of leflunomide compared with other DMARD. *J Rheumatol*. 2004; 31: 1906-1911.

Carvalho FR, Santos JS, Elias Junior J, et al. The influence of treatment access regulation and technological resources on the mortality profile of acute biliary pancreatitis. *Acta Cir Bras*. 2008; 23 suppl 1: 143-50, discussion 150.

Gardner TB, Vege SS, Chari ST, et al. The effect of age on hospital outcomes in severe acute pancreatitis. *Pancreatology*. 2008; 8: 265-270.

Han B, Gfroerer JC, Colliver JD. Associations between duration of illicit drug use and health conditions: Results from the 2005-2007 national surveys on drug use and health. *Ann Epidemiol*. 2010; 20: 289-297.

Ibanez L, Laporte JR, Carne X. Adverse drug reactions leading to hospital admission. *Drug Saf*. 1991; 6: 450-459.

Khoo TK, Vege SS, Abu-Lebdeh HS, Ryu E, Nadeem S, Wermers RA. Acute pancreatitis in primary hyperparathyroidism: A population-based study. *J Clin Endocrinol Metab*. 2009; 94: 2115-2118.

Krumberger J. What is the most current recommendation for analgesic agents and pain management in patients with pancreatitis and other obstructive gastrointestinal (GI) disorders? *Crit Care Nurse*. 1999; 19: 110-112.

Lankisch MR, Imoto M, Layer P, DiMagno EP. The effect of small amounts of alcohol on the clinical course of chronic pancreatitis. *Mayo Clin Proc*. 2001; 76: 242-251.

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Moolsintong P, Loftus EV,Jr, Chari ST, Egan LJ, Tremaine WJ, Sandborn WJ. Acute pancreatitis in patients with Crohn's disease: Clinical features and outcomes. *Inflamm Bowel Dis*. 2005; 11: 1080-1084.

Morris-Stiff G, Webster P, Frost B, Lewis WG, Puntis MC, Roberts SA. Endoscopic ultrasound reliably identifies chronic pancreatitis when other imaging modalities have been non-diagnostic. *JOP*. 2009; 10: 280-283.

Pelaez-Luna M, Vege SS, Petersen BT, et al. Disconnected pancreatic duct syndrome in severe acute pancreatitis: Clinical and imaging characteristics and outcomes in a cohort of 31 cases. *Gastrointest Endosc*. 2008; 68: 91-97.

Raimondo M. What is the role of EUS in screening for chronic pancreatitis? *Nat Clin Pract Gastroenterol Hepatol*. 2007; 4: 530-531.

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Sah RP, Pannala R, Chari ST, et al. Prevalence, diagnosis, and profile of autoimmune pancreatitis presenting with features of acute or chronic pancreatitis. *Clin Gastroenterol Hepatol*. 2010; 8: 91-96.

Sakorafas GH, Farnell MB, Farley DR, Rowland CM, Sarr MG. Long-term results after surgery for chronic pancreatitis. *Int J Pancreatol*. 2000; 27: 131-142.

Sakorafas GH, Farnell MB, Nagorney DM, Sarr MG, Rowland CM. Pancreatoduodenectomy for chronic pancreatitis: Long-term results in 105 patients. *Arch Surg*. 2000; 135: 517-23, discussion 523-4.

Spigset O, Hagg S, Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: Data from the world health organization (WHO) database of adverse drug reactions. *Int Clin Psychopharmacol*. 2003; 18: 157-161.

Tsiotos GG, Mullany CJ, Zietlow S, van Heerden JA. Abdominal complications following cardiac surgery. *Am J Surg*. 1994; 167: 553-557.

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

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Brown A, Young B, Morton J, Behrns K, Shaheen N. Are health related outcomes in acute pancreatitis improving? An analysis of national trends in the U.S. from 1997 to 2003. *JOP*. 2008; 9: 408-414.

Cheng RM, Mamdani M, Jackevicius CA, Tu K. Association between ACE inhibitors and acute pancreatitis in the elderly. *Ann Pharmacother*. 2003; 37: 994-998.

Dore DD, Seeger JD, Arnold Chan K. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Curr Med Res Opin*. 2009; 25: 1019-1027.

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Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. *Am J Gastroenterol*. 2006; 101: 2128-2138.

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Tam V, Frost SA, Hillman KM, Salamonson Y. Using administrative data to develop a nomogram for individualising risk of unplanned admission to intensive care. *Resuscitation*. 2008; 79: 241-248.

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Wu BU, Johannes RS, Kurtz S, Banks PA. The impact of hospital-acquired infection on outcome in acute pancreatitis. *Gastroenterology*. 2008; 135: 816-820.

Yang AL, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Arch Intern Med*. 2008; 168: 649-656.

3. Studies Excluded Due to Not Studying the Health Outcome of Interest

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Townsley CA, Pond GR, Oza AM, Hirte HW. Evaluation of adverse events experienced by older patients participating in studies of molecularly targeted agents alone or in combination (ref art 553333). *Clin Cancer Res*. 2006; 12: 2141-2149.

4. Studies Excluded Due to Not Being an Administrative Database Study

Allen DB. Safety of human growth hormone therapy: Current topics. *J Pediatr*. 1996; 128: S8-13.

Borkhuu B, Nagaraju D, Miller F, et al. Prevalence and risk factors in postoperative pancreatitis after spine fusion in patients with cerebral palsy. *J Pediatr Orthop*. 2009; 29: 256-262.

Dufour MC, Adamson MD. The epidemiology of alcohol-induced pancreatitis. *Pancreas*. 2003; 27: 286-290.

Fitzgerald GW, Thomas GW. Pancreatitis in northern Newfoundland and Labrador: A 20-year review of the Grenfell Regional Health Services experience. *World J Surg*. 1990; 14: 43-44.

Soran A, Chelluri L, Lee KK, Tisherman SA. Outcome and quality of life of patients with acute pancreatitis requiring intensive care. *J Surg Res*. 2000; 91: 89-94.

5. Studies Excluded Due to Data Source Not from the United States or Canada

Bagul A, Siriwardena AK. Evaluation of the Manchester classification system for chronic pancreatitis. *JOP*. 2006; 7: 390-396.

Evans JMM, Mcmahon AD, Steinke DT, Mcalpine RR, Macdonald TM. Do h2-receptor antagonists cause acute pancreatitis? *Pharmacoepidemiol Drug Saf*. 1998; 7: 383-388.

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

Type of Code	Code	Description
ICD-9	577.0	Acute pancreatitis
ICD-9	577.1	Chronic pancreatitis
ICD-9	577.2	Cyst and pseudocyst of the pancreas
ICD-9	787.03	Nausea or vomiting
ICD-9	789.0	Abdominal pain
ICD-9	789.60-789.69	Abdominal tenderness
CPT	82150	Serum Amylase
CPT	83690	Serum lipase