[Ze]ro-[B]urden [R]isk [A]ssessment: Test-Free Prediction of Clinical Trajectories Following Acute Pancreatitis

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INTRODUCTION

Acute pancreatitis (AP) is a clinically heterogeneous and increasingly prevalent condition, marked by rapid-onset pancreatic inflammation that can lead to a wide spectrum of outcomes. While many patients recover uneventfully, others, especially those with necrotizing pancreatitis, deteriorate rapidly and require intensive care unit (ICU) admission, or go on to develop chronic sequelae such as exocrine pancreatic dysfunction (EPD) and Type 3c diabetes mellitus (pancreaticogenic diabetes;T3cDM)[1–4]. Notably, new-onset diabetes following a single episode of AP affects 15-23% of patients, with higher rates observed among those with severe or necrotizing forms of the disease[5,6]. These outcomes often manifest months or even years after initial presentation, and their delayed but significant burden underscores the need for reliable long-term prognostication.

Despite this clinical importance, existing tools for AP risk stratification remain suboptimal. Traditional scoring systems such as Ranson's criteria, BISAP, and APACHE II require lab testing, imaging, or delayed clinical data that limit their use at the time of presentation[7,8]. Moreover, these scores were developed primarily for short-term triage and provide little to no predictive power for longer-term complications such as EPD or T3cDM[9]. The development of scalable, real-time, and low-burden approaches that can accurately forecast both acute deterioration and chronic progression using only routinely collected electronic health record (EHR) data remains a critical unmet need[10,11].

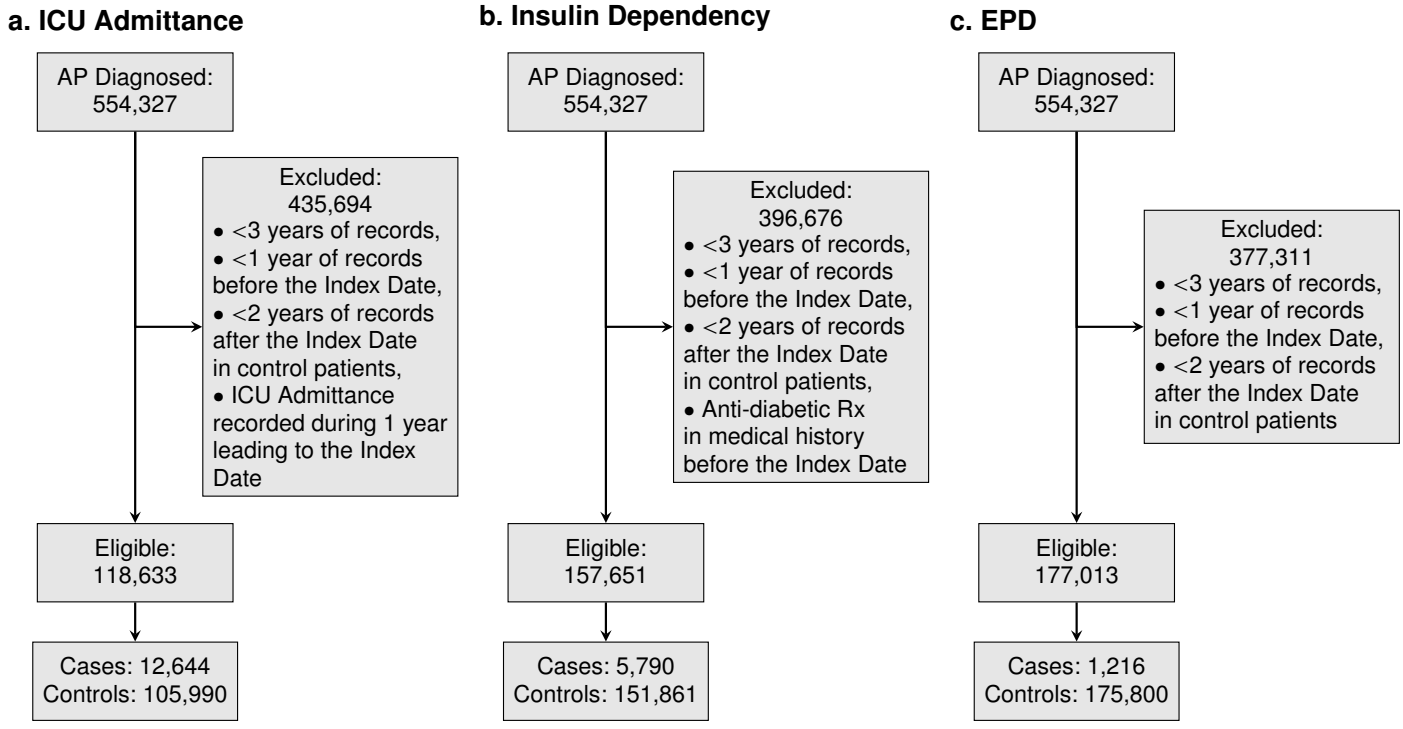

Fig. 1: CONSORT Diagrams for the three prognostic scenarios considered

TABLE 1: Patient Characteristics for three prognostic scenarios

ICU Admission ($n = 118,633$)	
Total patients	Control: 105,989 (89.3%), Case: 12,644 (10.7%)
Sex	Males: 53,352 (45.0%), Females: 65,281 (55.0%)
Mean age at screening	51 years 10 months
Other diseases of Pancreas (K86)	Case: 1,512 (12.0%), Control: 12,200 (11.5%)
Diabetes Mellitus (E08–E13)	Case: 5,131 (40.6%), Control: 29,268 (27.6%)
Oxygen Concentrator (E1390)	Case: 562 (4.4%), Control: 1,378 (1.3%)
Removal of calculi/debris from biliary/pancreatic duct(s) (43264)	Case: 263 (2.1%), Control: 2,111 (2.0%)
Critical Care Services (99291)	Case: 5,785 (45.8%), Control: 3,251 (3.1%)
Total patients	Case: 1,216 (0.7%), Control: 175,797 (99.3%)
Exocrine Pancreatic Insufficiency ($n = 177,013$)	
Total patients	Case: 1,216 (0.7%), Control: 175,797 (99.3%)
Sex	Males: 80,778 (45.6%), Females: 96,235 (54.4%)
Mean age at screening	53 years 8 months
Other diseases of Pancreas (K86)	Case: 612 (50.3%), Control: 25,913 (14.7%)
Diabetes Mellitus (E08–E13)	Case: 441 (36.3%), Control: 56,719 (32.3%)
ICU Admission	Case: 228 (18.8%), Control: 23,039 (13.1%)
Insulin Dependency ($n = 157,651$)	
Total patients	Case: 5,790 (3.7%), Control: 151,861 (96.3%)
Sex	Males: 69,887 (44.3%), Females: 87,764 (55.7%)
Mean age at screening	53 years 4 months
Other diseases of Pancreas (K86)	Case: 1,371 (23.7%), Control: 22,071 (14.5%)
Diabetes Mellitus (E08–E13)	Case: 4,546 (78.5%), Control: 34,448 (22.7%)
Oxygen Concentrator (E1390)	Case: 185 (3.2%), Control: 2,976 (2.0%)
Removal of calculi/debris from biliary/pancreatic duct(s) (43264)	Case: 168 (2.9%), Control: 7,201 (4.7%)
Critical Care Services (99291)	Case: 1,433 (24.7%), Control: 17,085 (11.3%)

In this study, we examine the applicability of the Zero-Burden Risk Assessment (**ZeBRA**) algorithm to the problem of precise, low-burden prognostic prediction in AP. At its core, **ZeBRA** is an AI-driven, disease-agnostic comorbidity pattern recognizer that analyzes the longitudinal structure of existing EHRs without requiring additional diagnostic effort[12–15]. Here we adopt the **ZeBRA** framework to predict three clinically salient outcomes following AP diagnosis: (i) ICU admission risk across multiple time horizons, from same-day to up to 12 months post-diagnosis, (ii) long-term onset of exocrine pancreatic dysfunction (EPD), and (iii) subsequent insulin dependence in patients without baseline diabetes, serving as a proxy for pancreatogenic diabetes. Across these prognostic outcomes, the models achieve strong predictive performance, with high out-of-sample validation area under the curve (AUC) values. Our findings represent, to our knowledge, the

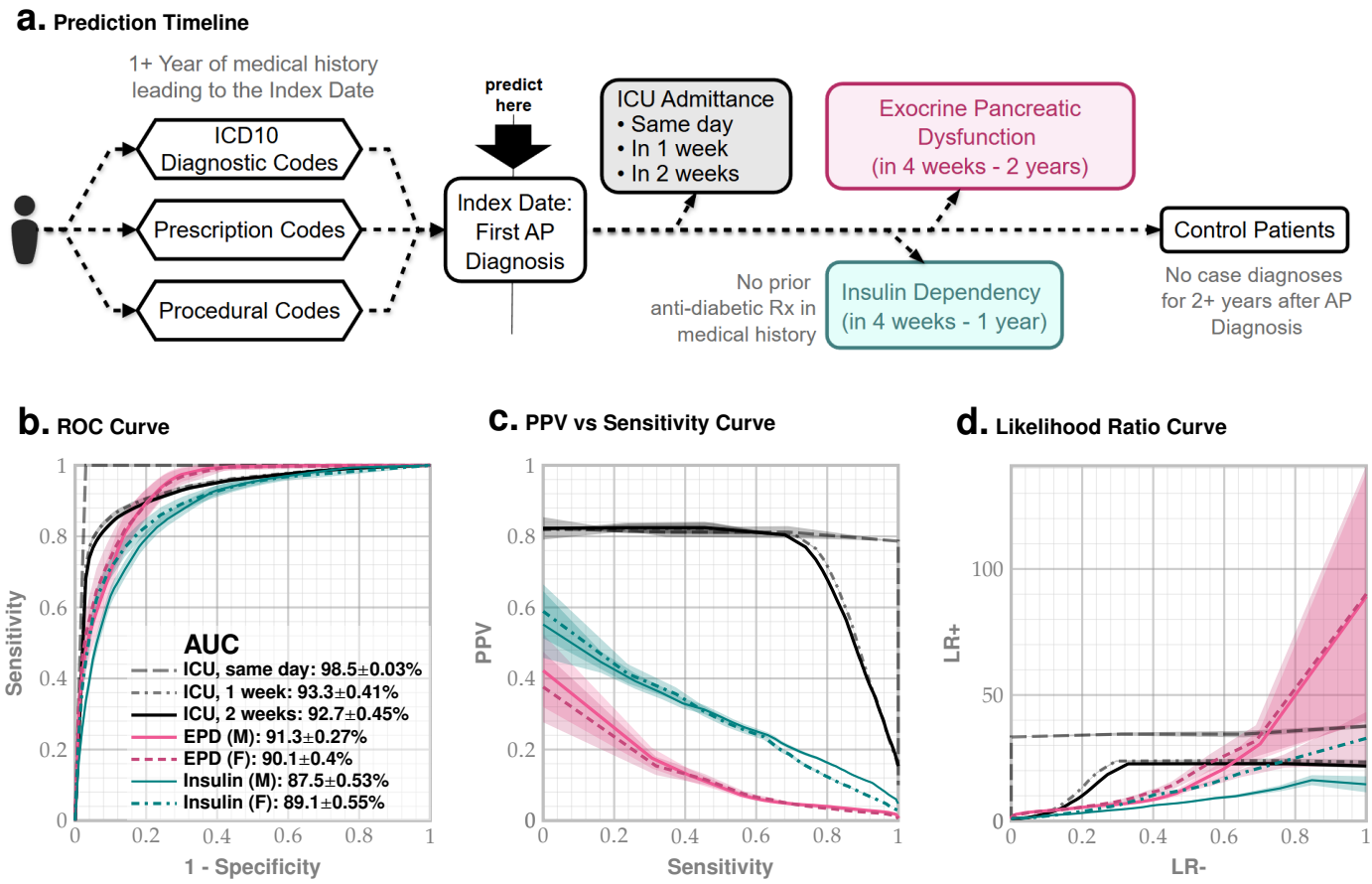

Fig. 2: **Prediction settings, horizons and predictive performance**. a, schematic reprresentation of prediction horizon and timeline, illustrating the input types used (limited to time-stamped diagnostic, procedural and prescription codes) b, Out-of-sample *i.e.* validation ROC curves c, PPV-Sensitivity curves d, Likelihood Ratio curves

TABLE 2: Out-of-sample Predictive Performance at 96% specificity with 95% CI*

Prediction Target	Sensitivity	PPV	ACC	NPV	LR+	LR-	AUC
ICU admittance same day	1.0 ± 0.0	0.796 ± 0.0	0.964 ± 0.0	1.0 ± 0.0	34.10 ± 0.0	0.0 ± 0.0	98.55±0.03
ICU admittance within 1 week	0.768±0.009	0.765±0.002	0.932±0.001	0.961±0.001	19.21±0.233	0.241±0.010	93.30±0.41
ICU admittance within 2 weeks	0.740±0.010	0.688±0.002	0.936±0.001	0.968±0.001	18.63±0.251	0.270±0.010	92.71±0.45
EPD (M)	0.386±0.011	0.539±0.007	0.898±0.001	0.929±0.001	9.841±0.278	0.638±0.011	91.30±0.27
EPD (F)	0.402±0.011	0.563±0.006	0.900±0.001	0.931±0.001	11.43±0.280	0.621±0.011	90.14±0.4
Insulin dependence (M)	0.395±0.011	0.545±0.007	0.899±0.001	0.930±0.001	10.12±0.280	0.629±0.011	87.46±0.53
Insulin dependence (F)	0.517±0.011	0.607±0.005	0.912±0.001	0.943±0.001	13.01±0.286	0.502±0.011	89.06±0.55

*Reported performance metrics include out-of-sample positive predictive value (PPV), negative predictive value (NPV), accuracy (ACC), and both positive likelihood ratio (LR+) and negative likelihood ratio (LR-), which respectively quantify the strength of a positive or negative test result in altering disease probability, and the area under teh receiver operating characteristic curves (AUC).

first retrospectively validated deep comorbidity-signature driven simultaneous forecasting of immediate and delayed prognostic outcomes of AP without expensive imaging, labs, or patient-reported data. Our findings support the feasibility of integrating ner zero-burden AI-informed tools directly into clinical workflows, enabling semi-contiunuous longitudinal risk monitoring in pancreatitis care.

Materials and Methods

ZeBRA is a significant reformulation of our past work on the disease-agnostic ZCoR algorithm[13–15], to predict short-term and long-term adverse outcomes in AP patients. **ZeBRA** uses structured EHR data as its only inputs in addition to demographic inforation, specifically timestamped diagnosis (Dx), medication (Rx), and procedural (Px) codes. Each patient is encoded as sequences of ICD10, CPT and NDC codes, which inform a range of engineered features designed fotr pattern discovery, as well as informing a custom 12-dimensional embedding. This feature-mapping encodes odds ratios of all observed codes with respect to a defined indication or prognostic outcome, which are then used to train a stack of Gradient Boosting Decision Tree classifiers[16]. As shown in the core framework, "channels" corresponding to Rx, Dx and Px are trained seprately, and finally brought together in a top-layer GBM. We trained three separate ZCoR prediction models for Insulin Dependency, EPD, and ICU Admittance, with number of trainable parameters ranging from 35 to 408 thousands depending on the prediction target (see Table 3).

#1. why not LLMs

Data Source. All predictive models in this study were trained and evaluated using the longitudinal administrative claims data from the Merative™ MarketScan® Commercial Claims and Encounters (CCAE) and Medicare (MDCR) databases. This dataset comprises de-identified insurance claims for over 164 million unique individuals enrolled in employer and government-sponsored health plans across the United States, over the years 2008-2024. The dataset captures multi-year, patient-level healthcare utilization records, including timestamped diagnostic codes (ICD-9/10-CM), procedural codes (CPT/HCPCS), and outpatient and retail prescription data (NDC codes), allowing for detailed temporal modeling of clinical trajectories.

Outcome Definition, and Inclusion/Exclusion Criteria. Acute pancreatitis (AP) cases were identified using ICD-10 codes K85.xx, with inclusion criteria requiring no prior AP diagnosis within a one-year lookback window to reduce contamination from recurrent or chronic disease. ICU admissions were ascertained from critical care billing codes (CPT G0390, G9657, 4168F, 99291) on the same day or subsequent to the index AP encounter. For long-term outcome modeling, exocrine pancreatic dysfunction (EPD) was defined by ICD-10 code K86.81. A proxy for AP-induced diabetes was constructed by identifying patients without preexisting diabetes or anti-hyperglycemic prescriptions who initiated insulin therapy within one year following AP diagnosis (see Table 4 for all codes used to define prediction targets). Each target phenotype was defined using strict inclusion and exclusion criteria (See Figure 1). Each patient's risk of post-AP adverse events was evaluated at the date of the first AP diagnosis recorded (Index Date), using at least 1 year of medical history leading to the Index Date. Patients with insufficient observation and prediction windows for each respective outcome were excluded to prevent temporal bias (See Figure 2a). Model training and evaluation were performed on non-overlapping patient subcohorts, and no future-label leakage was permitted.

Results

For ICU admission post-AP diagnosis, **ZeBRA** achieved AUCs of 98.6 ± 0.03 (same-day), 93.3 ± 0.41 (within one week), 92.71 ± 0.45 (within two weeks), and maintained high performance over broader intervals: 0.844 (2-4 weeks), 0.813 (4-8 weeks), and 0.775 (6-12 months). Long-term risk of EPD onset within 1 month to two years of index was predicted with AUC 91.30 ± 0.27 (male) and 90.14 ± 0.4 (female). In a distinct subcohort of initially non-diabetic patients, the transition to insulin dependence (from no record of any anti-diabetic medication) was predicted with AUC 0.921. All models used clinically defined case/control phenotypes and balanced validation. Positive likelihood ratios for the three scenarios were as follows: i) ICU admission 34.10 (same day), 18.63 ± 0.251 (within two weeks), ii) EPD 9.8 ± 0.28 (males) and 11.43 ± 0.28 (females) and iii) insulin dependency 10.12 ± 0.28 (males) and 13.01 ± 0.29 (females). Positive predictive values (PPV) ranged between 0.54 to $.80$, yielding highly precise actionable predictions on all three prognostic scenarios.

Discussion

In the United States, the incidence and burden of acute pancreatitis (AP) have risen steadily over the past two decades. Hospitalization rates increased from approximately 40 per 100,000 in the late 1990s to over 130,000 annual cases by the 2010s, making AP one of the most common gastrointestinal causes for inpatient admission[17]. In particular, the incidence of hypertriglyceridemia-induced AP (HTG-AP) has also shown marked growth, especially among Hispanic and non-Hispanic white adults[18]. These trends are consistent with global data showing a substantial increase in the absolute number of AP cases between 1990 and 2021, reflecting both demographic changes and evolving risk profiles[19,20]. Together, these data highlight both the persistent prevalence of AP and the growing contribution of metabolic factors to its etiology.

Chronic pancreatitis (CP) is characterized by progressive inflammation, irreversible pancreatic damage, abdominal pain, and complications such as exocrine insufficiency, diabetes mellitus, and pancreatic cancer[21–23]. Despite these clinical challenges, progress has been hampered by the absence of reliable biomarkers and prospective longitudinal data, limiting advances in diagnosis and therapeutic interventions[24]. Historically, CP research has focused predominantly on male populations with alcoholic CP, primarily from non-U.S. centers[25–31]. The only large-scale U.S. longitudinal study was conducted at the Mayo Clinic between 1976 and 1982[32]. Although these studies provided valuable insights into disease progression, predicting individual clinical trajectories remains challenging, particularly in early-stage CP where definitive morphological changes are often absent on imaging. Consequently, longitudinal data in patients with early disease are urgently needed[33–35].

Recently the etiological profile of CP has broadened beyond alcohol to include genetic, autoimmune, and environmental factors[34,35]. For example, hereditary pancreatitis and mutations in genes such as PRSS1 and CFTR have been identified as significant contributors[36]. Autoimmune pancreatitis, though relatively rare, has emerged as a distinct subtype with unique clinical and histological features[34]. There is growing recognition that CP represents a disease continuum, with overlapping stages and etiologies[37,38]. These insights highlight the need for diagnostic frameworks that account for the heterogeneity and multifactorial nature of CP.

Advances in imaging techniques, such as Magnetic Resonance Cholangiopancreatography (MRCP), have enabled the quantitative assessment of pancreatic fibrosis[39,40]. Endoscopic pancreas fluid collection combined with molecular analysis has broadened biomarker discovery efforts[41], while the clinical significance of pancreatogenic (Type 3c) diabetes has gained recognition[42,43]. Additionally, studies have identified an increased risk of osteoporosis and fractures in CP patients, although the mechanisms remain unclear[44–46]. Despite these advances, validated diagnostic criteria for early-stage CP and mechanistic models remain limited[21,47].

Current CP management is largely limited to symptomatic treatment[24]. While animal models have offered insights into disease pathogenesis, these findings have not translated into curative treatments or strategies to prevent progression. Major limitations include the difficulty of obtaining histological samples at early disease stages and the absence of prospective, well-characterized cohorts linked to electronic health records (EHRs).

The integration of artificial intelligence (AI) via the **ZeBRA** suite transforms the capabilities of the PROCEED study by addressing its current limitations and vastly amplifying its potential. While PROCEED has recruited 350 participants to date and provides invaluable prospective data with linked biospecimens, its relatively small sample size inherently limits the ability to identify and generalize rare but critical comorbidity patterns and progression pathways. In contrast, the retrospective datasets leveraged in this proposal—such as Merative Marketscan, Truveta, and the Colorado Biobank—offer access to millions of patient records spanning diverse geographic and demographic populations. This scale allows for the detection and analysis of nuanced comorbidity patterns and disease trajectories that would remain undetectable in smaller prospective cohorts.

AI-driven methods, including the proven **ZeBRA** suite, enable the extraction of meaningful insights from this vast retrospective data, identifying predictors of AP-to-CP transitions, diabetes onset, and ICU admission with unprecedented precision. These models are inherently data-driven, capable of uncovering complex, non-linear relationships across patient histories, treatment interventions, and outcomes, which are beyond the reach of conventional statistical analyses. Furthermore, the established success of the **ZeBRA** suite in other clinical domains[12–15] demonstrates its robustness and reliability, building confidence in its application to acute pancreatitis.

Here we have shown significant progress in this direction. A validdated **ZeBRA** suite will enable rapid, near-zero-burden point-of-care potentially universally deployable diagnostic tools, enabling real-time, personalized risk assessments, that can address gaps in early diagnosis, prognosis, and intervention planning for AP and CP patients.

Future work will implement prospective interventions based on this approach, in studies such as “PROspective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational StuDies: Rationale and Study Design for PROCEED” (PROCEED) study aims to address these challenges via a comprehensive framework for investigating chronic pancreatitis (CP) through a multi-center, prospective cohort study designed by the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)[48]. PROCEED aims to enroll patients across the CP spectrum using standardized criteria. Its primary goals are to define

disease progression, test the predictive value of candidate biomarkers, and establish a translational research platform. Participants include controls, suspected CP cases, and definite CP cases, with structured case report forms and protocol-driven evaluations at baseline and follow-up. A linked biorepository stores blood, urine, saliva, stool, pancreatic fluid, and pancreatic tissue samples.

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SUPPLEMENTARY INFORMATION

TABLE 3: Feature and Parameter Counts by Model

Model	# DX Features	# DX Trainable Parameters	# RX Features	# RX Trainable Parameters	# PX Features	# PX Trainable Parameters	# Total Trainable Parameters
ICU	6,612	25,622	980	18,310	4,186	24,388	68,320
Insulin	6,873	21,912	975	15,434	4,319	28,110	65,456
EPD	6,937	13,405	992	7,891	4,390	14,452	35,748

TABLE 4: Codes used to define prediction targets

Target	Codes
Acute Pancreatitis	ICD-10 Codes*: K85 K85.0 K85.00 K85.01 K85.02 K85.1 K85.10 K85.11 K85.12 K85.8 K85.80 K85.81 K85.82 K85.9 K85.90 K85.91 K85.92
ICU Admittance	CPT Codes**: G0390 99291 G9657 4168F
EPD	ICD-10 Code: K86.81
Insulin Dependency	NDC Codes*** for Insulin Prescriptions: 00002751001 00002751017 00002751099 00002751101 00002751199 00002751201 00002751299 00002751559 00002751601 00002751659 00002751699 00002771201 00002771227 00002771261 00002771401 00002771459 00002771461 00002771501 00002771559 00002771563 00002772801 00002773701 00002775201 00002775205 00002811001 00002811101 00002811201 00002814001 00002820705 00002821001 00002821101 00002821201 00002821305 00002821405 00002821501 00002821517 00002821591 00002821601 00002821759 00002822201 00002822259 00002822827 00002823301 00002823305 00002823505 00002824001 00002831001 00002831101 00002831201 00002831501 00002831517 00002831591 00002831759 00002834001 00002841001 00002841101 00002841201 00002841501 00002844001 00002850001 00002850101 00002851001 00002854001 00002861001 00002861501 00002864001 00002871501 00002871517 00002871591 00002871759 00002872559 00002873001 00002873059 00002877001 00002877059 00002879359 00002879459 00002879701 00002879759 00002879761 00002879801 00002879859 00002879899 00002879901 00002879959 00002879961 00002880359 00002880501 00002880559 00002882427 00002898005 00002951501 00003183310 00003183315 00003183410 00003183415 00003183510 00003183710 00003183715 00003244110 00003244510 00003352115 00024576105 00024576302 00024586903 00024587102 00024587490 00024588236 00024588463 00024589463 00024592410 00024592500 00024592501 00024592505 00024592605 00069005019 00069005053 00069005085 00069070737 00069072437 00088221900 00088221901 00088221905 00088222033 00088222052 00088222060 00088250033 00088250052 00088250205 00088502005 00088502101 00169001771 00169004471 00169004571 00169007011 00169010001 00169011101 00169020001 00169022201 00169030001 00169033301 00169183302 00169183311 00169183317 00169183318 00169183402 00169183411 00169183417 00169183418 00169183511 00169183702 00169183711 00169183717 00169183718 00169210011 00169210125 00169220011 00169220125 00169231321 00169231421 00169231721 00169244010 00169244210 00169244710 00169255013 00169255090 00169255097 00169266015 00169266090 00169266097 00169266211 00169291115 00169300301 00169300315 00169300325 00169300415 00169300425 00169300715 00169300725 00169320111 00169320415 00169320515 00169320611 00169320615 00169330312 00169347318 00169347418 00169347718 00169351215 00169352215 00169352815 00169355215 00169357215 00169368213 00169368512 00169368712 00169369619 00169633910 00169643210 00169643255 00169643810 00169643910 00169750111 00338012612 00403296118 00403344918 00955172801 00955172805 00955172901 23490668700 35356010200 47918087490 47918087890 47918088018 47918088236 47918088463 47918089190 47918089463 47918089818 47918090218 49502019580 49502019671 49502019675 49502025080 49502025171 49502025175 49502039380 49502039471 49502039475 49999099310 49999099410 50090035200 50090035300 50090040300 50090049700 50090049800 50090087600 50090127600 50090137500 50090139800 50090147500 50090166300 50090166400 50090166500 50090167800 50090219300 50090227200 50090227300 50090406800 50090408500 50090417700 50090450000 50090495500 50090495600 50090495900 50090539100 50090583500 50090617800 50090618400 50090639100 50090641400 50090643900 50090656500 54569165101 54569165102 54569165200 54569165202 54569231800 54569231801 54569231900 54569231901 54569255700 54569255701 54569281600 54569281700 54569289100 54569289101 54569291800 54569291801 54569291802 54569295100 54569295101 54569346700 54569346701 54569383300 54569383301 54569383302 54569383400 54569383401 54569383500 54569383501 54569383502 54569532100 54569560500 54569630000 54569630100 54569630101 54569643500 54569646200 54569646201 54569657000 54569658400 54569658500 54569658600 54569658700 54569662500 54569663000 54569663100 54868011200 54868142801 54868142901 54868208901 54868238001 54868274600 54868277700 54868347400 54868359800 54868361900 54868438100 54868462600 54868510800 54868520100 54868532700 54868532701 54868576500 54868582400 54868583600 54868588300 54868589900 54868605400 54868623100 55045350601 55045350801 55045360201 55045362401 55045368501 58016478801 59060183302 59060183402 59060183702 59060231404 59060231704 66143751005 66733077301 66733082201 66733082259 68115070905 68115072810 68115072905 68115074610 68115083910 68258598301 68258889903 68258892703 68258892803 68258893001 68258893103 68258896701 68258897701 68258898501 68258898601 73070010011 73070010210 73070010215 73070010310 73070010315 73070020011 73070020310 73070020315 73070040011 73070040315 73070050315 83257001411

*International Classification of Diseases, Tenth Revision[49]
**Current Procedural Terminology[50]
***National Drug Code Directory[51]